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November 18, 1998

Dr. C. W. Jameson
National Toxicology Program
Report on Carcinogens
79 Alexander Drive
Building 4401, Room 3127
Research Triangle Park, NC 27709

Reference: Supplemental Comments on NTP's Proposal for Listing Environmental Tobacco Smoke (ETS) in the Report on Carcinogens, Ninth Edition

Dear Dr. Jameson:

Philip Morris U.S.A. takes this opportunity to provide additional information and scientific commentary on the National Toxicology Program's (NTP) intent to review environmental tobacco smoke (ETS) for possible listing in the *Report on Carcinogens, Ninth Edition*, as noticed in 63 *Fed. Reg.* 5565, February 3, 1998.

For your information, the chronic inhalation study using RASS (room-aged sidestream smoke, an ETS surrogate) carried out in our laboratories and referenced at Tab 2B of our March 20, 1998, submission to your office has been published. It appears in *Inhalation Toxicology* 10(7):663-697, 1998.

In addition, Philip Morris U.S.A. submits an analysis of a relevant and recent publication from the International Agency for Research on Cancer (IARC) multicenter epidemiologic study of ETS exposure and lung cancer risk, which has appeared since our initial submission.

The review is of the first full publication, by Nyberg et al. (1998), from the Stockholm center of the IARC study (*See* Appendix 1). Despite the claim by the authors of that study that there is "an effect of adulthood ETS exposure on lung cancer risk, particularly for occupational exposure," a careful examination of the reported results suggests that a more appropriate conclusion would be that the data presented are "consistent with either a slightly elevated risk or no risk at all" (IARC Monograph, 1986.) None of the point estimates reported by Nyberg et al. (1998) is statistically significant. In addition, the claim is made that an association between reported ETS exposure and lung cancer was particularly evident for occupational exposure; however, this conclusion is not supported by data from recent exposure measurement studies (e.g., Phillips et al., 1996).

Systematic biases are reportedly examined and ruled out by Nyberg and co-authors, although analysis of this claim demonstrates that evidence for misclassification and differential recall bias is present. Nyberg et al. claim that the association of ETS exposure and lung cancer risk achieves statistical significance when reported exposure in ongoing and current, but the epidemiologic literature does not provide support for this assertion. Nyberg et al. also report "no evidence" for an association of lung cancer risk with childhood ETS exposure. In general this observation is consistent with the majority of published studies that investigated this association. The authors did not publish the criteria upon which their findings of "no evidence" was based. Nyberg et al. do not discuss how this reported finding diminishes the consistency arguments regarding their stated positions on adults.

More recently, Boffetta et al. published the IARC "Multicenter Case-Control Study of Exposure to Environmental Tobacco Smoke and Lung Cancer in Europe" (*See* Appendix 2). The Nyberg et al. (1998) publication reviewed here was one of the centers in the IARC study (reported by Boffetta et al.) Therefore, the Nyberg et al. (1998) data are incorporated in the IARC multicenter study, and the reported results of the IARC study would clearly provide a more definitive and representative assessment of the risk purportedly associated with exposure in ETS. The IARC multicenter study, being one of the largest ETS studies of its kind, reports no statistically significant overall increased association between reported exposures to ETS and lung cancer risk. Consequently, these recent and more definitive human data do not support the classification of ETS as a human carcinogen.

We believe the review described above and the recent publication by Boffetta et al. of the "Multicenter Case-Control Study of Exposure to Environmental Tobacco Smoke and Lung Cancer in Europe" will be of assistance to your reviewers in their scientific deliberations.

Sincerely,

Richard A. Carchman, Ph.D.
Vice President
Research, Development & Engineering

Submission by Philip Morris U.S.A.

to

The National Toxicology Program

- Appendix 1 -

Comments on Nyberg et al., 1998

November 18, 1998

Comments on: "Environmental Tobacco Smoke and Lung Cancer in Nonsmokers: Does Time Since Exposure Play a Role?" F. Nyberg, V. Agrenius, K. Svartengren, C. Svensson, and G. Pershagen, *Epidemiology* 9: 301-308, 1998

Executive Summary

We have reviewed the first full publication from one of the centers which took part in the International Agency for Research on Cancer (IARC) multicenter epidemiologic study investigating a possible association of exposure to environmental tobacco smoke (ETS) with lung cancer (Nyberg et al., 1998b). Despite the authors' claim that there is "an effect of adulthood ETS exposure on lung cancer risk, particularly for occupational exposure," a more careful examination of the reported results suggests that a more appropriate conclusion would be that the data presented are "consistent with either a slightly elevated risk or no risk at all" (IARC, 1986). None of the point estimates reported by Nyberg et al. (1998b) is statistically significant. In addition, the claim is made that an association between ETS exposure and lung cancer was particularly evident for occupational exposure; however, this conclusion is not supported by actual exposure measurement studies (e.g., Phillips et al., 1996). Systematic biases are reportedly examined and ruled out by Nyberg and coauthors, although analysis demonstrates that important evidence for misclassification and confounders is present. Finally, Nyberg et al. claim that the association of ETS exposure and lung cancer risk achieves statistical significance when exposure is ongoing and current, but the epidemiologic literature provides no support for this assertion.

Introduction

The publication by Nyberg et al. presents the results from the Stockholm center of the IARC multicenter case-control study of environmental tobacco smoke (ETS) and lung cancer risk. The study base was composed of Swedish-speaking persons 30 years or older who were resident in Stockholm County from October 1, 1989, to September 30, 1995, and who were in a physical and mental condition permitting a 1-hour interview. Self-reported regular smokers were excluded from the study base, regular smoking being defined as having smoked more than 1 cigarette/day, 10 cigarettes/week, 40 cigarettes/month, 4 cigarillos/week, 3 cigars/week, or 4 pipes/week for one year or longer. Cases were obtained from three hospitals in Stockholm, which would include all lung cancer cases, since once lung cancer is suspected, all patients in the Stockholm area are transferred to one of those three hospitals. For 96% of the cases, histologic or cytologic slides were reviewed by a pulmonary pathologist for validation of the original diagnosis. Controls from the Stockholm County population register were frequency-matched approximately 2:1 to cases in strata defined by gender, age, and three hospital catchment areas.

All cases were interviewed personally. Controls were interviewed either personally or by telephone. The percentage split of the two interviewing procedures for controls was not specified. A trained physician or nurse interviewed subjects using a structured questionnaire. Six interviewers were used, and all six interviewed both cases and controls. Two main interviewers performed 76% of the interviews. The questionnaire contained questions regarding occasional smoking, a residential history, a lifetime occupational history, and a food frequency assessment of

foodstuffs rich in retinol, carotene, and vitamin C. Exposure to ETS was assessed using a core questionnaire developed on the basis of a study on urinary cotinine and ETS exposure (Riboli et al., 1990). It covered recollections of childhood exposure, estimates of domestic exposure from spouse and other cohabitants, and exposure at all workplaces, at other places, and in vehicles. Exposure to known or suspected occupational lung carcinogens was evaluated based on all occupations in the working history, classified as to occupational code ISCO-68 and industrial code ISIC-71.

Statistical analysis of ETS exposure considered different sources and environments as well as time of exposure. Numbers of pipes and cigars smoked were converted to cigarette equivalents using a factor of three. No reference was provided for this conversion factor. Odds ratios (OR) and 95% confidence intervals (CI) were calculated from multiple unconditional logistic regression, adjusted for matching variables: gender, age in five categories, and catchment area. All results were adjusted for the following potential confounders using multiple logistic regression: occasional smoking (three categories), vegetable consumption (three categories), degree of urban residence during the past 35 years (three categories), and years of work in risky occupation (continuous).

Of the 145 eligible lung cancer cases, 8.3% were identified at autopsy or died before interview, while 6.2% refused participation, giving a total non-response rate of 14.5%. This resulted in 124 enrolled cases. The total non-response rate among controls was 17.1%, resulting in a total of 235 self-reported never-smoking controls.

Major results of the study can be summarized as follows. For all of these results, the total number of male cases was 35, and the total number of female cases was 89. The number of exposed (ETS) cases (N) is provided after each OR.

TABLE I

Exposure Metric	**Gender**	**OR**
Spousal (spouse smoker)	Men	1.96 (95% CI, 0.72-5.36) (N = 13)
	Women	1.05 (95% CI, 0.60-1.86) (N = 50)
	Both	1.17 (95% CI, 0.73-1.88) (N = 63)
Spousal (reported exposure to smoking spouse)	Men	1.64 (95% CI, 0.59-4.51) (N = 12)
	Women	0.94 (95% CI, 0.53-1.67) (N = 46)
	Both	1.05 (95% CI, 0.65-1.68) (N = 58)
Exposed at work	Men	1.89 (95% CI, 0.53-6.67) (N = 30)
	Women	1.57 (95% CI, 0.80-3.06) (N = 67)
	Both	1.61 (95% CI, 0.91-2.85) (N = 97)
Exposed in other indoor locations	Men	1.31 (95% CI, 0.50-3.38) (N = 11)
	Women	0.90 (95% CI, 0.44-1.86) (N = 16)
	Both	0.94 (95% CI, 0.54-1.63) (N = 27)
Exposed in vehicles (non-work related):	Men	1.71 (95% CI, 0.49-5.98) (N = 6)
	Women	0.41 (95% CI, 0.09-1.75) (N = 9)
	Both	0.98 (95% CI, 0.41-2.37) (N = 15)

Nyberg et al. also carried out a number of calculations investigating possible dose-response relationships as well as calculations designed to elucidate the potential temporal effects of exposure on the ORs. These results will be discussed more fully below.

This analysis will be organized to focus on several key aspects of the publication. These are: (i) the overall results, (ii) the reported gender differences, (iii) dose-response relationships and differential recall bias, (iv) reported differences between the ORs for spousal and workplace exposure, (v) adjustment for confounding, and (vi) reported temporal effects of exposure.

(i) Overall Results

Nyberg et al. calculated ORs for seven types of exposure; namely, spouse smoker, reported exposure to smoking spouse, exposed at work, exposed in other indoor locations, exposed in vehicles (non-work related), childhood exposure to smoking father, and childhood exposure to smoking mother. The ORs for all of these exposures, except for the last two, have already been summarized above. Since both Nyberg et al. and the summary of the IARC multicenter study published in the 1996-1997 IARC Biennial Report (Boffetta et al., 1997) state that no elevated relative risk was observed for childhood exposure, the results relating to exposure during childhood will not be discussed herein.

The first point to be noted is that **none** of the reported ORs was statistically significant at the 95% level. Therefore, on the basis of this study alone, the conclusion would be that the epidemiologic data are consistent with the null hypothesis; namely, that reported exposure to ETS is not associated with an increased risk of lung cancer. On the other hand, it may be argued that the point estimate of 1.17 for both genders combined for lung cancer associated with "spouse smoker," despite not being statistically significant, is consistent with recent meta-analyses of the

reported association of ETS exposure and lung cancer (Hackshaw et al., 1997). It is important to note, however, that these meta-analyses are subject to the same systematic biases -- confounding, misclassification of smoking status, and differential recall bias -- that most likely affect the Nyberg et al. results and which will be discussed below. There is, however, a large difference between the OR for both genders combined when spousal exposure is determined using the exposure measure "spouse smoker" (OR = 1.17), and the exposure measure "reported exposure to smoking spouse" (OR = 1.05). This difference is equivalent to a 70.6% smaller risk estimate. Nyberg et al. have chosen to report the higher of the two results in their abstract, despite the fact that this result is not based on reported exposure. It should be noted that in the recent publication which reports the full IARC multicenter results (Boffetta et al., 1998), "reported exposure to smoking spouse" was the exposure measure chosen.

The second point is that, with the exception of exposure in the workplace and spouse smoking, the point estimates for women were less than 1.0. In all cases, however, ORs for men were elevated. The fact that women made up the majority of the total sample, 71.8%, results in the risk estimate for both genders combined being quite modest. Therefore, the cited relative risk for spousal exposure can be attributed completely to the reported increased risk in males. This reported difference between men and women is discussed in more detail in the next section.

(ii) Gender Differences

There are, in principle, at least three possible explanations for the difference between men and women reported in the Swedish study. The first is that there is indeed a real difference between genders with respect to the proposed association of ETS exposure and lung cancer. Although most of the published epidemiologic data regarding ETS exposure and lung cancer are for women, for those studies which did investigate both genders no clear pattern emerges. Of particular interest are the larger, more recent studies cited in the table below. The numbers of exposed (ETS) cases (N) is provided after each OR.

TABLE II

OR (RR)		
Men	**Women**	**Reference**
0.75 (95% CI, 0.31-1.78) (N = 44)	0.75 (95% CI, 0.47-1.20) (N = 144)	Janerich et al., 1990
1.10 (95% CI, 0.6-1.8) (N = 101)	1.20 (95% CI, 0.8-1.6) (N = 164)	Cardenas et al., 1997
1.60 (95% CI, 0.67-3.82) (N = 39)	1.08 (95% CI, 0.60-1.94) (N = 67)	Kabat et al., 1995
1.10 (95% CI, 0.60-2.03) (N = 72)	1.10 (95% CI, 0.72-1.68) (N = 185)	Schwartz et al., 1996

In only one of these four studies is the OR or RR for men greater than that for women. If there were a real difference between the two genders, such a trend would be expected from these studies. Clearly, this is not the case.

The second possible explanation is that there is a systematic bias in the Nyberg et al. study that differentially increases the ORs for men but not for women or differentially decreases the ORs for women. One candidate for such a systematic bias would be misclassification of smoking status. Lee and Forey (1995) (a study supported by Philip Morris) summarize a large number of studies that have investigated misclassification of smoking status using repeat interviews; overall, they suggest that 14% of men and 5% of women claiming to be never-smokers during a second interview reported that they had been current or former smokers during a first interview conducted some years before. Therefore, it appears that men may be three times more likely to misrepresent their smoking status than are women. Nyberg et al. rule out misclassification as a bias in their study based on an earlier publication (Nyberg et al., 1998a), which investigated potential misclassification in the Stockholm sample using next-of-kin interviews. In this publication, they cite a total misclassification rate of 2.4% (interestingly enough, seven women and one man, not at all consistent with the general published finding (Lee and Forey, 1995) that men are more likely to misrepresent their smoking than are women). The next-of-kin interview method, however, would appear to be an imprecise tool to measure misclassification, since of the 26 self-reported occasional or former smokers in the sample used in that publication, 57.7% of next-of-kin indicated that the individuals were never-smokers.

Even this explanation, however, would fail to account for more than a maximum of 25% of the difference (P.N. Lee, personal communication). Therefore it would appear that the third explanation is the most likely; namely, that the reported difference is solely due to chance. Examination of the two sets of ORs reveals that the difference is not statistically significant. (For

example, the p-value for the difference between men and women using the category "spouse smoker" is 0.29, and the p-value for the category "reported exposure to smoking spouse" is 0.35). This is yet another example demonstrating that epidemiology can be a relatively "blunt instrument" which cannot reliably detect meaningful effects when the reported differences between cases and controls are small (Breslow and Day, 1980). Clearly the definition of "small" is variable, depending on the number of subjects in the case and control groups and the number of systematic biases which affect the results. Therefore, the elevated ORs reported for males in comparison to those of females are most likely simply a chance occurrence, and by extension the small reported elevated risk for the entire sample is most likely a chance occurrence. This interpretation is underscored by the very wide confidence limits. A difference in ORs for spousal ETS exposure between men and women is also reported by Boffetta et al. (1998) in the IARC multicenter study. In this case, the reported difference was less, with OR = 1.47 for men (95% CI, 0.81-2.66, n = 23) and OR = 1.11 for women (95% CI, 0.88-1.39, n = 321).

Although Nyberg et al. do not explicitly address the reported difference in ORs between men and women until their Conclusion section, they do present some hypotheses in their Discussion section which could be taken as an explanation for their findings. They point out that smoking prevalence in many western societies has declined among men over the last decades but has increased among women. Although this statement may appear to be intuitively correct, their supporting data are from the Phillips et al. (1996) personal ETS exposure study in Stockholm; those researchers were able to recruit only 10 men and 11 women with home exposure for their study. However, this fact in no way addresses why the OR for such an exposure should be different for the

two genders, since a potentially increased OR for the association of lung cancer with ETS exposure is a function of the difference between exposure among the cases and controls and has nothing to do with the absolute number exposed. Nyberg et al. go on to state that, "[o]ur data also indicate that the average amount smoked at home among currently smoking men married to never-smoking women has decreased over the last decades, whereas the opposite is true for women." However, no data are presented. This would appear to be simply a *post hoc* attempt to rationalize a difficult-to-explain observation without actual supporting data. However, there are data in Phillips et al. (1996) which do provide information on current personal exposure by gender. For home exposure of working subjects, median ETS-derived respiratory suspended particulate (RSP) is 0.20 $\mu g/m^3$ for men and 0.21 $\mu g/m^3$ for women, while median nicotine levels are 0.08 $\mu g/m^3$ for men and 0.07 $\mu g/m^3$ for women. For workplace exposure, median ETS-derived RSP is 0.45 $\mu g/m^3$ for men and 0.53 $\mu g/m^3$ for women, while median nicotine levels are 0.16 $\mu g/m^3$ for men and 0.18 $\mu g/m^3$ for women. These differences are not statistically significant. There were also no reported differences in cotinine levels as a function of gender. It would appear, therefore, that the published data on current exposures provide little basis for the authors' suggestion that exposure in the home for men is higher than exposure for women (Phillips et al., 1996).

(iii) Reported Dose-Response Trends and Differential Recall Bias

In Table 3 of the publication, Nyberg et al. present ORs as a function of the reported "dose level" from spousal exposure estimates. Four metameters of "exposure" are used -- cigarettes/day, years exposed, hour-years exposed, and pack-years exposed -- and the sample population is divided into three groups -- unexposed, "moderately" exposed, and "significantly" exposed. For all four of the metameters, the "moderately" exposed group has an OR which is unchanged or reduced as compared to the unexposed group, but the "significantly" exposed groups have increased ORs, although none of them is statistically significant. There is no discussion of the possible role of differential recall bias; however, in Nyberg et al. (1998a), the authors stated that, "for 11 next-of-kin reporting some regular smoking by the spouse, the index subject (seven cases, four controls) reported markedly higher cumulative amounts." The fact that significant differences exist in the recall of exposure to ETS as a function of who is being asked has been observed in a number of studies, and these studies have recently been summarized by LeVois and Switzer (1998).

Clearly, there is no reason to assume that next-of-kin reporting of exposure is more reliable than that of the index subject himself. (As a matter of fact, based on the results of next-of-kin interviews dealing with misclassification of smoking status, such data may be even less reliable.) On the other hand, Nyberg et al. had chosen to regard information from next-of-kin interviews as meaningful; therefore, dose-response trends should be calculated on the basis of both reports. The fact that the cumulative amounts were higher should not affect the duration metameter, but the other three metameters will be affected. As noted above, Nyberg et al. (1998a) reported that next-of-kin

interviews failed to confirm high ETS exposure for seven of the cases and four of the controls. Therefore, the ORs can be recalculated for each of the three affected metameters, resulting in the following table. (It should be noted that in constructing the table below it is necessary to take into account that next-of-kin were interviewed for only one-half of the controls. Therefore, in making the adjustment it is necessary to move 7 cases from the "significantly" exposed group to the "moderately" exposed group, but to move 8 controls. One might expect that such a change -- moving more controls than cases -- would actually accentuate the dose-response trend; however, as can be seen from the table, such is not the case.)

TABLE III

Variable	OR Based on Subject Report*	OR Based on Next-of-Kin Report**
Average daily exposure from spouse		
Unexposed (ref.)	1	1
< 10 cig./day	0.96	0.99
> 10 cig./day	1.16	0.96
Total duration of exposure		
Unexposed (ref.)	1	1
< 30 years	1.01	1.01
> 30 years	1.14	1.14
Total weighted duration		
Unexposed (ref.)	1	1
<90 hour-years	0.85	0.92
>90 hour-years	1.25	1.03
Cumulative reported exposure		
Unexposed (ref.)	1	1
<9 pack-years	0.84	0.90
>9 pack-years	1.53	1.36

* Nyberg et al., 1998b.

** ORs recalculated from data taken from Nyberg et al., 1998a.

As can be seen from the above table, using the correction stated for cumulative exposure based on the next-of-kin validation study, any evidence for a purported dose-response trend is extremely weak. Also, it is clear from the above table that, even at the high exposure, the OR

ranges from 0.96 for "cigarettes/day," consistent with no association, to 1.36 for "pack-years," suggestive of at best a weak association. Therefore, one needs to ask the question, is there any way to determine what the "right" metameter should be? This question can perhaps be answered in the following way. The true measurement of "exposure" or "dose" is the concentration to which one is exposed integrated over the time exposed. However, neither metameter is by itself adequate, since for hour-years, there is no measurement of the actual amount smoked during that period of time (concentration), while for pack-years, there is no measurement of the actual time of exposure. Therefore, there is no substitute for the careful measurement of the actual exposure. The importance of measurement has been emphasized in several publications (IARC, 1986; NRC, 1986; Meridian, 1988; NHMRC, 1995).

In light of the claim frequently made (see, e.g., Davis, 1997) that the highest OR for the association of ETS exposure with lung cancer is always observed at the highest exposure level, it is interesting to see if there is observed consistency in the literature when two metameters of exposure are used. The following table summarizes these data using "cigarettes per day" and "years of exposure."

TABLE IV

Study	Relative Risk (Cigs/Day)	Significance (linear trend)*	Relative Risk (Yrs of Exposure)	Significance (linear trend)*
Akiba et al., 1986	1.0, 1.3, 1.5, 2.1	No	1.0, 2.1, 1.5, 1.3	No
Humble et al., 1987	1.0, 1.8, 1.2	No	1.0, 1.6, 2.1	No
Koo et al., 1987	1.0, 2.3, 1.7, 1.2	No	1.0, 2.0, 1.4, 2.3	No
Geng et al., 1988	1.0, 1.4, 2.0, 2.8	No	1.0, 1.5, 2.2, 3.3	No
Kalandidi et al., 1990	1.0, 1.5, 1.8, 1.6	No	1.0, 1.3, 1.3, 2.0, 1.9	No
Du et al., 1993	1.0, 0.7, 1.5	Yes	1.0, 1.4, 1.1	No
Cardenas et al., 1997	1.0, 1.4, 1.4, 0.6	No	1.0, 1.5, 1.3, 1.2	No
Wang et al., 1996	1.0, 0.4, 1.4, 1.4	No	1.0, 1.4, 1.1, 1.1	No

* Trend test performed with exclusion of the unexposed group. If the unexposed group is included, both results reported in the Geng et al. study have a statistically significant trend, but the Du et al. result for cigarettes per day is no longer statistically significant. It should also be noted that although the trend test for Du et al. is statistically significant, it is based on only two points.

Of the 16 results shown above, only seven of them report the highest relative risk at the highest exposure level. Moreover, only one of the seven studies (Geng et al.) is internally consistent, reporting the highest relative risk at the highest exposure level using both metameters. Also, none of these studies attempted to evaluate the potential effect that differential recall bias may have had at higher exposure levels. These data suggest that dose-response does not appear to be consistently reported for ETS exposure and lung cancer risk.

(iv) Reported Differences Between Spousal and Workplace Exposure

The one clearly elevated OR reported by Nyberg et al. for women, although still not statistically significant, involved workplace exposure. The OR for men continued to numerically exceed that for women, but the difference was less striking. Nyberg et al. (1998b) rationalize this result as follows:

> Our study shows a clearer lung cancer effect for variables measuring ETS exposure in the work place. Individual monitoring also indicates that in Sweden today, work and home ETS exposure are of similar intensity for those exposed, but work exposure is more common. [Ref. 30 in Nyberg] If recent ETS exposures are biologically most relevant, less misclassification may result with variables of work exposure. This possibility offers one explanation for the unexpectedly higher RRs observed for work exposure than for spousal ETS exposure in this and several other studies. [Refs. 3-5, 9, 31-33 in Nyberg]

It is important to closely examine the claims made in this paragraph. The first claim is that individual monitoring indicates that in Sweden today, work and home ETS exposure are of similar intensity for those exposed. This statement is referenced to the Philips et al. study (1996), but it is not in agreement with the results Philips et al. reported. The Stockholm personal monitoring study reports that the ratio of ETS particles, as measured by the tobacco-specific marker solanesol, between smoking homes and smoking workplaces was 5.4. The ratio of nicotine between smoking homes and smoking workplaces was somewhat less, being only 3.2. Even the nicotine value, however, suggests a much greater exposure to ETS in a smoking home than in a smoking workplace. It is also interesting to note that the previous publication by Nyberg et al. (1998a) cites a combined

OR of 1.48 (uncorrected for misclassification, 1.41 corrected) (95% CI, 0.89-2.46) for workplace exposure to ETS for the combined sample from Stockholm (115 cases), Barcelona (45 cases), and Rome (15 cases). The fact that this OR is lower than the OR from Stockholm itself mathematically (OR = 1.61, not statistically significant) suggests that in particular the OR for workplace ETS exposure from Barcelona was lower than the OR for workplace ETS exposure from Stockholm. However, the levels of ETS exposure in the workplace in Barcelona are reportedly much greater than those in Stockholm (Phillips et al., 1997). Therefore, for at least these two centers, there is no agreement between the reported ORs for workplace ETS exposure and the level of current measured exposure. This inconsistency could be a consequence of either the considerable uncertainty in the reported ORs (note the lack of statistical significance) or of some as yet unknown bias.

The second claim made by Nyberg et al. is that work exposure is more common; that is, that there are a greater number of individuals exposed at the workplace than at home (although for those people exposed in both locations, time spent away from work is certainly greater than time spent at work). This point is confirmed by the Phillips et al. study (1996), but it is also certainly irrelevant. The fact that it is more common is reflected in the number of cases (and the number of controls) exposed, and has no effect whatsoever on the ORs. The only factor that affects the ORs would be the differential exposure between cases and controls.

Nyberg et al. also claim that their report of a higher OR for workplace exposure than for spousal exposure is in agreement with a number of other studies. In total, seven references are cited. Of these seven studies, only one of them (Wu-Williams et al., 1990) reports an OR for

workplace exposure which is statistically significantly higher than the OR for spousal exposure. Two of these studies, Brownson et al. (1992) and Kabat et al. (1995) actually report lower ORs for workplace exposure as compared to spousal exposure. Three studies, Fontham et al. (1994), Shimizu et al. (1988), and Wu et al. (1985), report slightly higher ORs for workplace exposure as compared to spousal exposure. Finally, Schwartz et al. (1996) report a relatively large increase, but it is not statistically significant. There are four studies not cited by Nyberg et al., which clearly report lower ORs for workplace as compared to spousal exposure (Garfinkel et al., 1985; Koo et al., 1987; Zaridze et al., 1994; Wang et al., 1996). In addition, Boffetta et al. (1998) report essentially the same OR for spousal exposure (1.16) as for workplace exposure (1.17).

In summary, therefore, there is no adequately supported scientific explanation for the conclusion by Nyberg et al. that workplace exposure is associated with higher ORs than is spousal exposure. This reported finding is not in line with the literature on personal exposure monitoring, nor does it have consistent corroboration in the epidemiologic literature. The only remaining explanation is, once again, that the reported difference has occurred by chance.

It is worthwhile emphasizing the importance of having reliable exposure data in order to evaluate properly the results of epidemiologic studies on ETS exposure and lung cancer. In the 1986 IARC Monograph on Tobacco Smoke, the summary of the section on the possible association of ETS exposure and lung cancer makes this same point:

> Several epidemiological studies have reported an increased risk of lung cancer in nonsmoking spouses of smokers, although some others have not. In some studies, the risk of lung cancer in nonsmokers increased in relation to the extent of spouses' smoking. Each of the studies had to contend with substantial difficulties in determination of passive exposure to tobacco smoke and to other possible risk factors for the various cancers studied. The resulting errors could arguably have artefactually depressed or raised estimated risks, and, as a consequence, each is compatible either with an increase or with an absence of risk. As the estimated relative risks are low, the acquisition of further evidence bearing on this issue may require large-scale observational studies involving **reliable measures of exposure** both in childhood and in adult life. (p. 308, emphasis added.)

(v) Adjustment for Confounding

Nyberg et al. indicate that all results were adjusted for the matching variables, gender, age, and catchment area, as well as for occasional smoking, occupational exposure, urban residence, and diet. They indicate that they further evaluated confounding by these latter factors in various models, using different categorical and continuous metrics, without finding any indication of confounding. Since they present no data with respect to either the potential confounders investigated nor the models they used, the reader must take this statement at face value.

There is one potential confounder, however, which merits further discussion: namely, occasional smoking. The Stockholm sample included 36 individuals who were defined as occasional smokers (20-408 packs on an occasional basis, or 0.05 to 1.12 pack-years). It is somewhat unusual to include occasional smokers in a study designed for never-smokers, since it is highly likely that an

individual who self-reports occasional smoking may well have understated his or her total smoking. In addition, it would be anticipated that inclusion of occasional smokers in the study would tend to bias the results away from the null, because of the much higher relative risk associated with active smoking and lung cancer. However, Nyberg et al. point out that adjusting for occasional smoking as a potential confounder had no effect on the reported ORs. This point is not at all surprising, given the fact that of the 36 occasional smokers, 12 were in the case group while 24 were in the control group. Since there were more occasional smokers in the control group than in the case group, inclusion of these occasional smokers would certainly not bias the results away from the null. However, inclusion of these occasional smokers does not appear to bias results toward the null, either. This observation is quite surprising, as can be seen from the following brief analysis.

If a proportion $\underline{s}$ of the population smokes, if the relative risk of lung cancer in smokers is $\underline{R}$, and if a proportion $\underline{p}$ of smokers deny smoking, one can estimate that the proportion of smokers among self-reported non-smokers will be $p_0 = ps/(1-s+ps)$ in the general population (controls) and will be $p_1 = Rps/(1-s+Rps)$ in lung cancer cases. For small p, p_1/p_0 is approximately equal to R; i.e., one would expect the proportion of misclassified individuals to be of order R times higher in the cases. Of course, if misclassification is only of very long term ex-smokers of small amounts, R will be only slightly greater than 1, so the proportions will be similar in cases and controls. Also, the comparative numbers smoked by each group could influence the value of R. Despite the above two caveats, Nyberg et al. are left with the conclusion that there is clearly no association between occasional smoking and lung cancer risk. It is then difficult to justify the use of the same data to suggest an association between ETS exposure and lung cancer risk.

(vi) Reported Temporal Effects of Exposure

Perhaps the most novel claim reported by Nyberg et al. is that the ORs for all exposures combined increase as a function of the time since last exposure. These results are presented in Table 5 where it can be seen that as time of last exposure diminishes from >15 years, to 3-15 years, to 0-2 years, the ORs increase for cumulative exposure in hour-years and for duration of exposure measured in years. For the most recent exposures the ORs range from 1.87 to 2.27, depending on level and metameter of exposure. None of these ORs is statistically significant, however, undoubtedly because the sample size of the most recently exposed group is quite small (consistent with the wide confidence interval), and there is no evidence of a dose-response trend. In addition, the three ORs in each grouping are not statistically different from one another.

There is insufficient information in the literature to provide further corroboration of this proposed temporal effect. Nyberg et al. quote two other studies. Akiba et al. (1986) reported a relative risk of 1.8 (95% CI, 1.0-3.2) for "current exposure" (0-9 years) and 1.3 (95% CI, 0.9-2.4) for "former exposure" (>10 years). Hirayama (1990) reported a relative risk of 1.45 (95% CI, 1.04-2.02) for "recently exposed" and 1.36 (95% CI, 0.85-2.18) for "non-recently exposed" cases. Again none of these ORs is statistically different from any other.

There is simply not enough information to determine if the temporal effect that Nyberg et al. report is real or is simply a chance occurrence. Nor do the authors provide sufficient information to carry out a more thorough analysis of the data. Boffetta et al. (1998) also claim that

there is a temporal effect, although the data are much less compelling. They report an OR of 0.92 for exposure which ceased more than 15 years before, 1.20 for exposure which ceased 3-15 years before, and 1.18 for current exposure and exposure which ceased up to two years before. There is no evidence of a statistically significant dose-response trend, and the reported temporal effect is quite weak. It would be of interest to determine to what extent the Swedish data have contributed to this reported result.

Summary

Nyberg et al. end their publication with the statement that, "[i]n conclusion, we found evidence of an effect of adulthood ETS exposure on lung cancer risk, particularly for occupational exposure." The question is, do the data support that conclusion? We believe that the above analysis clearly demonstrates that the data do not support that conclusion for the reasons articulated herein. The data demonstrate no elevated level of risk for women, the large majority of the total sample, as a consequence of reported spousal exposure. The reportedly elevated OR for men is not explained by a demonstrated difference in exposure over time, nor is there any support in the published literature for there being a difference in purported risk as a consequence of gender. The elevated risk reported for workplace exposure is not consistent with the data from a recent monitoring study, cited by Nyberg et al., nor is it consistent with data derived from another IARC study center, that is, Barcelona. Lastly, there is clearly no evidence of a dose-response trend when differential recall bias is taken into account. Overall, the best interpretation of the Nyberg et al. (1998) data is that they do not demonstrate an elevated risk for self-reported ETS exposures.

Moreover, virtually all of the published ETS/lung cancer studies fall into the above category; that is, consistent with either a slightly elevated risk or no risk at all. The studies which do report statistically significant results are, for the most part, small and therefore likely to be subject to significant systematic errors. The point has been made, however, that the majority of studies do report an elevated risk, and even though most do not achieve statistical significance, the overall result cannot be explained by chance. When looked at from the perspective of only random error (chance events), this is correct. However, this point can be explained by the presence of relatively small and difficult to detect systematic biases. It is anticipated that it would take many years of fundamental research to truly explore all of the possible biases and confounders which occur in such studies.

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Submission by Philip Morris U.S.A.

to

The National Toxicology Program

- Appendix 2 -

Boffetta et al., 1998

November 18, 1998

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National Toxicology Program
Report on Carcinogens Group

Boffetta P, Agudo A, Ahrens W, Benhamou E, Benhamou S, Darby SC, Ferro G, Fortes C, Gonzalez CA, Jöckel K-H, Krauss M, Kreienbrock L, Kreuzer M, Mendes A, Merletti F, Nyberg F, Pershagen G, Pohlabein H, Riboli E, Schmid G, Simonato L, Trédaniel J, Whitley E, Wichmann H-E, Winck C, Zambon P, Saracci R. 1998. Multicenter case-control study of the exposure to environmental tobacco smoke and lung cancer in Europe. J Natl Cancer Inst 90(19):1440-1450.

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Lung Cancer and Exposure to ETS in the Household and in the Workplace:

Additional Analyses of the Data from a Negative Study, Brownson et al. (1992)

Post Hearing Comments to:
Docket Office, Docket No. H-122 Room N-265
U.S. Department of Labor
200 Constitution Ave., NW
Washington, DC 20210

Submitted by:
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September 1, 1995

TABLE OF CONTENTS

EXECUTIVE SUMMARY

The studies of Brownson et al. (1992) and Fontham et al. (1994) are the two largest case-control studies of lung cancer and environmental tobacco smoke (ETS) in non-smokers. In its preliminary quantitative risk assessment of ETS, the Occupational Safety and Health Administration (OSHA) relied solely on the results of the study by Fontham et al. to the total exclusion of the study by Brownson et al. (OSHA, 1994, pg 15995) There is no scientific basis for this choice. Indeed, it is preferred to use the information from all the relevant epidemiologic studies. In its revised risk assessment, OSHA should expand its consideration of the scientific literature from the single study by Fontham et al. to the results of all the epidemiologic studies. In such an evaluation, the results from the study by Brownson et al. (1992) should receive consideration and weight at least as high as that given to the study by Fontham et al. (1991, 1994).

OSHA incorrectly reports that the Brownson study indicates a positive association between lung cancer and ETS exposure. (OSHA, 1994, pg 15993) All the data and findings reported by Brownson et al. indicate that this is a ***negative*** study; that is, there is no association between lung cancer and ETS exposure in non-smoking women. Specifically, Brownson et al. (1992; pg 1526-1527) report:

> "no elevated lung cancer risk associated with passive smoke exposure in the workplace."
>
> "little evidence of increased cancer risk associated with passive smoke exposure in childhood"
>
> "When analyses were limited to direct interviews, no clear pattern of increase or decrease in risk estimates was apparent (for adult household and spousal ETS exposures)"

It is unclear how OSHA can conclude this is a positive study when the authors themselves report no association of lung cancer with ETS exposure at the workplace, at the home during adulthood or during the home during childhood. These negative findings appear to have been overlooked by OSHA in favor on a single quote in the abstract regarding the isolated, elevated risk of 1.3 in the highest adult and spousal exposure categories:

> "Adult analyses showed an increased lung cancer risk for lifetime nonsmokers with exposure of more than 40 pack-years from all household members (odds ratio [OR] = 1.3; 95% confidence interval [CI] = 1.0,1.8) or from spouses only (OR = 1.3; 95% CI = 1.0, 1.7) ... Ours and other recent studies suggest a small but consistent increased risk of lung cancer from passive smoking."

The data from the Brownson study were acquired from the National Cancer Institute and examined to further elucidate the findings of this study. Analyses were executed on the reported absence of an association of lung cancer risk with both workplace and household ETS exposure.

Results are presented here by the type of interview of the case: direct (that is, with the case herself) and surrogate (that is, with the next-of-kin of the case). Surrogate interviews are expected to provide less reliable and valid information than direct interviews because the next-of-kin may not have direct knowledge of the facts regarding the case's household and workplace ETS exposures. In epidemiologic research, "surrogate interview data is usually presumed to differ in quality from interview data obtained directly from the subject." (Rothman, 1986, pg 249) Estimates of risk based upon the direct interviews are expected to be more reliable than the estimates based on the surrogate interviews. Preference for direct interviews is also indicated by NCI's stated goal that this study obtain direct interviews for at least 60% of the cases.

Analyses of these data by type of interview of the case are also responsive to questions and

comments from Dr. Steven Bayard of the USEPA regarding this author's previous submission (Butler, 1994) to OSHA on the Brownson study. Specifically, Dr. Bayard posed questions regarding this author's analyses of the pattern of association between workplace ETS exposure and lung cancer and whether the pattern of association depended on the type of interview (direct or surrogate) of the cases. (Bayard, 1995, pg 14722)

The association between lung cancer and spousal smoking status for those with direct interviews is summarized below:

	Direct Interviews			
Spousal Smoking	Lifetime Never Smokers		Former Smokers	
(pack-years)	OR*	95% CI	OR*	95% CI
0	1.0	-	1.0	-
0 < < 15	1.0	0.6, 1.7	0.9	0.4, 2.1
15 ≤ < 40	0.7	0.4, 1.2	0.5	0.2, 1.2
40 ≤	1.0	0.6, 1.6	0.8	0.3, 1.7

* Adjusted for age, previous lung disease, and former smoking (4 levels; see text)

These results support the statement by Brownson et al. (1992, pg 1526) that "(w)hen analyses were limited to direct interviews, no clear pattern of increase or decrease in risk estimates was apparent (for spousal ETS exposure)." As shown above, among lifetime never smokers and former smokers, there is no increased risk of lung cancer associated with spousal ETS exposure.

The increased risk of lung cancer risk reported by Brownson et al. for those with ≥ 40 pack-years of exposure occurs only among those with a surrogate interview (see main text) and not among

those with the more reliable direct interviews. This pattern suggests that the elevated risk reported by Brownson et al. in the highest exposure group is an artefact of unreliable and invalid data obtained from surrogate interviews. This interpretation is strengthened by the observation that there is no pattern of increased risk among subjects with surrogate interviews if their spousal ETS exposure occurred in the recent past (within 15 years). The increased risk is observed only among subjects with surrogate interviews if their entire period of spousal ETS exposure occurred in the distant past ($\geq$ 15 years ago). Higher relative risks among those whose spousal ETS exposure ceased $\geq$ 15 years ago is not consistent with a causal relationship between ETS and lung cancer but is consistent with the poorer recollection of events that occurred long ago.

The association between lung cancer and workplace ETS exposure for those with direct interviews is summarized below:

	Direct Interviews			
	Lifetime Never Smokers		Former Smokers	
Workplace ETS	OR*	95% CI	OR*	95% CI
Never	1.0	-	1.0	-
Ever	1.1	0.8, 1.7	0.3	0.2, 0.6
Hours/Day-Years (Quartiles)				
0	1.0	-	1.0	-
Lowest	0.8	0.4, 1.6	0.2	0.1, 0.8
2	0.9	0.4, 1.7	0.4	0.1, 1.0
3	1.6	0.9, 2.9	0.4	0.1, 1.1
Highest	1.2	0.6, 2.2	0.3	0.1, 1.0

* Adjusted for age, previous lung disease, and former smoking (4 levels; see text)

These results support the finding of Brownson et al. (1992, pg 1527) that "there was no elevated lung cancer risk associated with passive smoke exposure in the workplace." As shown in the

above table, the omnibus comparison of "Never vs Ever" workplace ETS exposure generated odds ratios of 1.1 and 0.3 for lifetime never smokers and former smokers, respectively. The negative association observed for former smokers is statistically significant and is not consistent with an increased risk of lung cancer being associated with ETS exposure. Among lifetime never smokers, the two highest exposure groups have odds ratios greater than 1.0, but these values are not statistically significant. (p-value for trend = 0.29) Further, the highest risk is found among those who reported that their workplace ETS exposure occurred in the more distant past ($\geq$ 15 years ago), a pattern more consistent with recall bias than with a causal relationship between ETS and lung cancer.

In summary, the results of these analyses provide additional evidence on the absence of an association between lung cancer and ETS as reported by Brownson et al. (1992). These data further elucidate the recall bias that is the source of the elevated risk for ETS only among those with surrogate interviews. These data also provide further support for the finding of Brownson et al. (1992) on an absence of an association between workplace ETS exposure and lung cancer. In its revised risk assessment, OSHA should give substantial consideration and weight to these findings from one of the two largest case-control studies of ETS and lung cancer.

INTRODUCTION

Brownson et al. (1992) and Fontham et al. (1994) are the two largest case-control studies of the association between lung cancer and exposure to environmental tobacco smoke (ETS) among non-smoking women. The two studies are of approximately the same size. Brownson has a slightly larger total sample size than Fontham while Fontham has a slightly larger number of lung cancer cases:

	Brownson et al. (1992)	Fontham et al. (1994)
Number of Subjects	2,020	1,906
Number of Cases	618	653
Number of Controls	1,402	1,253

Compared to the more than 30 other epidemiologic studies on this topic, these two studies are generally superior in terms of larger sample size (each has a sample size approximately three times greater than any other study); completeness of information on potential confounders; exclusion of other sources of bias; and overall study design, protocol, and reporting.

In the preliminary quantitative risk assessment presented in its Notice of Proposed Rulemaking (NPR) on Indoor Air Quality, OSHA relied solely on the results of the study by Fontham to the total exclusion of the study by Brownson. (OSHA, 1994, pg 15995) There is no scientific basis for this choice. Indeed, it is preferred to use the relevant information from all the epidemiologic studies. In its revision of the NPR, OSHA should expand its consideration of the scientific literature from the single study by Fontham to all the epidemiologic studies on this topic. In such an evaluation, the results from the Brownson study should receive consideration and weight

at least as high as that given to the Fontham study.

Further, Fontham et al.'s (1991, 1994) estimate of the relative risk for workplace ETS is of suspect validity for at least two reasons. First, their estimates of the relative risks associated with workplace and household ETS exposure are inconsistent with each other. Fontham et al. (1994) estimates a relative risk of 1.4 for workplace ETS exposure but a lower relative risk of only 1.2 for household ETS exposure. However, among married non-smoking workers in the U.S. labor force, the average household ETS exposure is estimated to be a factor of approximately four *greater* than the average workplace ETS exposure. (Riboli et al., 1990; Butler, 1995b) If ETS were the source of the elevated relative risks reported by Fontham et al., then a higher relative risk is expected for household ETS exposure than for workplace ETS exposure. Because the reverse is found, the findings in Fontham et al. are not consistent with ETS being the source of increased lung cancer risks observed among those with workplace or household ETS exposure.

Second, Fontham et al. (1994) report a crude relative risk for workplace ETS exposure of only 1.1 (95% confidence interval = 0.9, 1.4) compared to an adjusted relative risk of 1.4 (95% CI = 1.1, 1.7). Most of the magnitude of the excess risk ascribed to workplace ETS exposure and its statistical significance depends on the validity of the adjusted estimate. This adjustment is based on a multiple logistic regression model that includes 10 potential confounding factors. Control for these potential confounders is not only desirable but is necessary given the small magnitudes of association being examined for ETS exposure and the crude methods of measuring ETS exposure. However, small spurious associations can be generated in such multiple logistic repression analyses if individual confounders are not correctly parameterized. Fontham et al. did not present the information on the magnitude or direction of the adjustment provided by any of these 10 factors. Without such information, it is impossible to independently evaluate the reasonableness of their multiple logistic regression. Thus, there is no assurance that the adjusted estimate of 1.4 for workplace ETS is not a statistical artifact of their complex adjustment process. Because of the absence of supporting information to evaluate the adjustment methods used by

Fontham el al., it is not possible to confirm the validity of either their multi-variable adjustment or their adjusted estimate of the risk associated with workplace ETS exposure.

OSHA incorrectly reports that the Brownson study indicates a positive association between lung cancer and ETS exposure. (OSHA, 1994, pg 15993) All the data and findings reported by Brownson et al. indicate that this is a ***negative*** study; that is, there is no association between lung cancer and ETS exposure in non-smoking women. Specifically, Brownson et al. (1992) report:

> "no elevated lung cancer risk associated with passive smoke exposure in the workplace." (pg 1527)
>
> "little evidence of increased cancer risk associated with passive smoke exposure in childhood" (pg 1526)
>
> For adult exposure, an odds ratio of 1.0 (95% confidence interval = 0.8, 1.2) for Never vs Ever exposure from all household members, and an odds ratio of 0.9 (95% CI = 0.8, 1.1) for Never vs Ever exposure to spousal smoking (pg 1528).
>
> For adult household exposure, an elevated relative risk of 1.2-1.3 for only those in the highest ($\geq$ 40 cigarette pack-year) exposure group that is balanced by decreased relative risks as low as 0.7 in the two intermediate exposure groups; that is, no consistent dose-response relationship. These small positive and negative relative risks reach statistical significance for some combinations of exposure metrics and sub-populations. (Table 2, pg 1527)

> "When analyses were limited to direct interviews, no clear pattern of increase or decrease in risk estimates was apparent (for adult exposures)" (pg 1526)....."We found fairly minor alterations in risk estimates when analyses were restricted to directly interviewed cases." (pg 1529)

All of the findings reported by Brownson et al. (1992) lead to the conclusion that this is a ***negative*** study. The last set of quotes indicate that Brownson et al. (1992) interpret the patterns of risks reported for adult exposures (their Table 2, both direct and surrogate interview) as presenting "no clear pattern of increase or decrease in risk estimates." However, these negative findings appear to have been overlooked by OSHA in favor of a single quote in the abstract regarding the isolated, elevated risk of 1.3 in the highest adult and spousal exposure categories:

> "Adult analyses showed an increased lung cancer risk for lifetime nonsmokers with exposure of more than 40 pack-years from all household members (odds ratio [OR] = 1.3; 95% confidence interval [CI] = 1.0,1.8) or from spouses only (OR = 1.3; 95% CI = 1.0, 1.7) ... Ours and other recent studies suggest a small but consistent increased risk of lung cancer from passive smoking."

Though the first sentence in the above statement is true, the conclusion is not supported by the data because of the absence of a dose-response pattern and the statistically significant decrease in risk in the intermediate exposure categories. Further, as quoted above, Brownson et al. acknowledge that "(w)hen analyses were limited to direct interviews, no clear pattern of increase or decrease in risk estimates was apparent (for adult exposures)."

To further elucidate the findings of the study by Brownson et al. (1992), this submission presents new analyses of these data as well as provide additional background on the analyses in the published report. Particular attention is focused on the presence of an elevated risk only in the highest exposure categories, the absence of a dose-response, the consistent presence of

decreased relative risks in the intermediate exposure categories, and the absence of an association of lung cancer with ETS exposure when analyses are restricted to direct interviews.

In addition, this submission provides analyses that respond to questions and comments from Dr. Steven Bayard of the USEPA and others regarding this author's previous submission (Butler, 1994) to OSHA on the Brownson study. Specifically, Dr. Bayard posed questions regarding this author's analyses of the pattern of association between workplace ETS exposure and lung cancer and whether the pattern of association depended on the type of interview (direct or surrogate) of the cases. (Bayard, 1995, pg 14722) The data set provided by NCI in 1994 was not complete and, specifically, did not contain information on type of interview. NCI has subsequently released further material that is sufficient to address the questions posed by Dr. Bayard as well as to provide additional analyses relevant to OSHA's interpretation of the results of this study.

The sharing of the Brownson case-control data set is consistent with NCI's stated policy of making data sets publicly available after NCI has conducted and published its planned analyses. (Alavanja, 1995a) The sharing of data is also encouraged by epidemiology societies so that research findings can be replicated. (International Epidemiology Association, 1990; Society for Epidemiologic Research, 1989) Also, the largest epidemiologic society in the United States recommends that "when epidemiologic data are relevant to the governmental decision-making process, including public policy and regulatory decisions, investigators should share the data tapes and records as promptly and expeditiously as possible..." (Society for Epidemiologic Research, 1990). The National Research Council (1985; pg 26) also recommends that research "data relevant to public policy be shared as quickly and widely as possible" and that "investigators should share their data by the time of publication of initial major results of analyses of the data except in compelling circumstances."

Consistent with the recommendations of these two epidemiologic societies, with NCI's policy and with the National Research Council, Fontham et al. must make available all of the data from their

study so that others can execute independent statistical and epidemiological analyses of them. These additional independent analyses are needed to verify and examine in greater depth the findings reported by Fontham et al. As is demonstrated in the statistical analyses presented in this submission, the amount and detail of the information from an epidemiologic study that is published in a peer reviewed journal may not be a sufficient summary of all the data from that study that is relevant to the development of public policy and regulatory decisions. The access of OSHA and others to the data used for public policy should not be limited by the editorial policies and page limitations of scientific journals nor by investigators' refusal to share data that were collected at public expense.

METHODS

The methods used in the Brownson study are presented by the primary researchers in a number of articles. (Alavanja et al, 1995b; Brownson et al, 1992). The methods and results of the analyses of the association between lung cancer and workplace ETS exposure have already been presented by this author to OSHA. (Butler, 1994) Only a brief summary of the design of this case-control study is presented here.

Data Collection: Cancer cases were identified through the Missouri Cancer Registry. The 618 lung cancer cases included in the study consist of White Missouri women, aged 30-84 years, who were diagnosed with primary lung cancer between January 1986 and June 1991 and who were either lifetime never smokers or former smokers who had stopped smoking at least 15 years.

The 1402 controls were matched by age group to cases at an approximate 2.2 to 1 ratio. For ages less than 65 years, controls were selected from the driver's license roster maintained by the Missouri Department of Revenue. For ages 65 to 84 years, controls were selected from the roster of Medicare recipients maintained by the Health Care Finance Administration.

Interviews were conducted by telephone and solicited information on household and workplace smoking as well as a number of demographic, nutritional, lifestyle, household radon and health history variables. Interviews were conducted personally (direct) with each of the 1402 controls and with 216 of the cases. Due to either ill health or death, interviews were conducted with next-of-kin surrogates for 402 of the cases.

Exposure to ETS from adult household and spousal smoking is measured in pack-years of exposure as well as pack-years x hours/day. Exposure to ETS in the workplace is measured in hours/day-years. (Brownson et al. 1992; Butler, 1994) A greater percentage of the cases than controls have missing values for these variables. This is due to some surrogate interviewees for the cases not being able to provide the requested information.

Statistical Analyses: Logistic regression models are used to examine the association between lung cancer and ETS exposure during adulthood in the home or at the workplace. This is the same statistical model used by Brownson et al. (1992). The exposure categorizations used here for household ETS exposure (cigarette pack-year: 0, $0< <15$, $15\leq < 40$, ≥ 40) and workplace ETS exposure (hours/day-years: 0 and quartiles of exposure) are the same as those used by Brownson et al. The computer diskettes provided by NCI in 1995 contain variables for each of these ETS exposures.

Previous analyses presented by this author confirmed and expanded upon Brownson et al.'s report of the absence of an association between lung cancer and workplace ETS exposure. (Butler, 1994) Dr. Steven Bayard questioned whether these negative findings reported both by Brownson et al. (1992) and Butler (1994) applied to cases with direct interviews and/or to those with surrogate interviews. Analyses to address Dr. Bayard's question are presented here. Dr. Bayard argued that interview information obtained directly from the case was more reliable than that obtained from a next-of-kin (surrogate). Thus, the estimates of risk based upon the direct

interviews would be more reliable than the estimates based on the surrogate interviews. This reasoning is consistent with NCI's stated (but unachieved) goal that this study obtain direct interviews for at least 60% of the cases (Survey Research Associates, 1992, pg 6).

Surrogate interviews occurred only among the cases. No surrogate interviews occurred among the controls.[1] In the examination of the patterns of association related to type of interview, the cases with direct interviews are compared to all controls, and the cases with surrogate interviews are also compared to all controls. Thus, the same controls are used for both comparisons. The use of the controls for the analyses stratified by type of interview of the case is consistent with Brownson's use of all the controls for comparison with cases that had direct and surrogate interviews. It is also consistent with the context of Dr. Bayard's question regarding the consistency of findings by type of interview.

Per this author's previous submission (Butler, 1994), analyses for workplace ETS exposure are presented using two different definitions of the unexposed groups. One analysis uses all subjects with no workplace ETS exposure, and the second analyses uses only subjects who have worked outside the home for at least six months and did not have workplace ETS exposure. The control groups differ in that the latter excludes women who did not work outside the home for six months or longer.

The results of the analyses based on all women can be compared to those from other epidemiologic studies like Fontham et al. (1994) who used the same definition for her comparison group. The analyses based only on women who worked outside the home benefit from the removal of potential confounding from factors associated with ever working outside the home

[1] All the initial telephone interviews with the controls were direct interviews. A second stage of data collection included a visit to the control's home at which time the control was asked to complete a self-administered questionnaire. A surrogate completed this self-administered questionnaire for a small number of the controls.

but suffer from the reduction of sample size in the unexposed group. The previous submission by this author reported substantial differences in results between these two comparison groups that was the result of a substantial positive risk of lung cancer associated with having not worked outside the home. (Butler, 1994) However, as explained below, this previously reported counter-intuitive direction of risk appears to be an artefact of the type of interview of the case and not a reflection of a causal or a self-selection factor. This distortion could not have been identified in this author's previous submission to OSHA because NCI had not provided the data on the type of interview for the cases.

In addition to analyses on workplace ETS exposure, analyses are also presented here on household ETS exposure during adulthood. These analyses were not possible with the data set provided by NCI in 1994. Consistent with Dr. Bayard's suggestion for workplace ETS exposure, analyses of household ETS exposure are executed according to the type of interview (direct or surrogate). Brownson et al. (1992, pg 1526) performed such analyses and reported that "(w)hen analyses were limited to direct interviews, no clear pattern of increase or decrease in risk estimates were apparent." These findings are confirmed and expanded upon in the analyses presented here.

The logistic regression models presented here adjust for age ($\leq$ 66, 67-73, 74-78, 79$\leq$) and previous lung disease (Yes vs No). Some analyses also control for former active smoking with a dichotomous variable (that is, Former vs Never) as was used by Brownson et al. (1992). In addition, some analyses control for former active smoking with a four level categorization that is based on intensity, duration and time-since-quit active smoking as defined below:

Level	Former Active Smoking		
	Intensity/ Duration		Time-Since-Quit
1.	< 15 pack-years	and	> 25 years
2.	< 15 pack-years	and	15 years ≤ < 25 years
		or	
	≥ 15 pack-years	and	> 25 years
3.	≥ 15 pack-years	and	15 years ≤ < 25 years
4.	Smoked > 100 cigarettes but never smoked regularly for > 1 year or Smoked 0 < < 100 cigarettes in their lifetime		

Level 1 of this variable consists of former regular smokers who have relatively lower intensity/ duration and longer time-since-quit. Level 1 is used as the baseline group for former smokers[2]. Level 3 consists of former regular smokers who have relatively greater intensity/ duration and shorter time-since-quit. This group is expected to be have relatively greater risk associated with their former smoking. Level 2 is expected to be intermediate in exposure between Levels 1 and 3. Level 4 consists of occasional smokers.

This more detailed categorization of former smoking is expected to remove a greater amount of the confounding than is possible with the single dichotomous variable that was used by Brownson et al. (1992) and Alavanja et al. (1995b). The use of this more refined variable also allows the examination of the amount of bias in the risk estimates for ETS exposure due to confounding that was not removed with the use of the simpler Never vs Former parameterization. This bias is referred to as "residual confounding" because it is the confounding (bias) that remains in the

[2] The lifetime never smokers serve as the baseline group when calculating the risk for the entire group of former smokers.

risk estimates (for ETS exposure) after the incomplete parameterization of the risk associated with the confounding factor. (Rothman, 1986, pg 108)

Information on duration and/ or intensity of former active smoking was missing for 44 cases and 6 controls. These subjects could not be reliably placed into any of these four levels of former active smoking and, thus, were excluded from the statistical analyses that used this 4-level variable. Almost all (41 of 44) of the former smoking cases with missing information have surrogate interviews.

In addition, the patterns of risk associated with household ETS exposure are compared between those whose household ETS exposure stopped at least 15 years ago and those whose household ETS exposure continued into the last 15 years. This comparison addresses the expected decline in lung cancer that would be realized by the elimination of household ETS exposure if, in fact, such an exposure posed a risk of lung cancer. If household ETS exposure is a cause of lung cancer, then those whose exposure ceased more than 15 years ago are expected to exhibit lower risks of lung cancer than those whose household ETS exposure continued into the last 15 years.[3] Such comparisons are made controlling for the subject's duration and intensity (pack-years) of household ETS exposure. This analysis is referred to as the comparison of 'time-since-quit' for household ETS exposure. An analysis of time-since-quit for workplace ETS exposure is also executed. By the same logic, if workplace ETS exposure is a cause of lung cancer, then those whose workplace ETS exposure continued into the last 15 years are expected to exhibit greater risks of lung cancer than those whose exposure stopped at least 15 years ago. [4]

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[3] The absence of a decline in risk among those with longer times-since quit suggests that any observed association with duration/ intensity is not causal. However, the presence of a decline in risk with longer time-since-quit does not in and of itself prove causation because the source of the observed decline with time-since-quit may be due to changes in other lung cancer risk factors that are associated with the cessation of ETS exposure.

[4] See previous footnote.

Three potential confounding variables are included in some statistical analyses here that were not reported in the analyses presented by Brownson et al. (1992): 4-level categorization for former active smoking; time-since-quit for household ETS exposure; and time-since quit for workplace ETS exposure. As is shown below, the odds ratios for all these variables do not reach statistical significance in all the logistic regression analyses in which they are used to control confounding. However, the failure to reach statistical significance is not a basis to delete a confounder from a multivariate analysis if the presence of the confounder substantially affects the risk estimate for the factors under study. Standard epidemiologic texts warn against such decisions:

> *"Hence, known confounding variables should be included in the equation regardless of the statistical significance if such inclusion changes the estimated coefficients of the risk variables by an appreciable degree."* (Breslow and Day, 1980, pg 225; emphasis in the original)

> Should we perform a statistical test to assess confounding? The answer to this question from the epidemiologic literature on confounding .... has been an unqualified *no* ..." (Kleinbaum, Kupper and Morgenstern, 1982, pg 254; emphasis in the original)

As is shown below, these three variables control for confounding and also elucidate the magnitude and pattern of association in these data. Thus, these variables are included in some logistic regression models despite the fact that they do not always reach statistical significance.

Using the data from this study, Alavanja et al. (1995b) estimated the percentage of lung cancer deaths among non-smoking women that is attributable to spousal smoking status. In generating these estimates, Alavanja et al. (1995b) categorized spousal smoking status as a dichotomous variable: < 40 cigarette pack-year vs ≥ 40 cigarette pack-years. Alavanja et al. did not present estimates of the percentage of lung cancers that are attributable to workplace ETS exposure.

The algebraic formulas to calculate attributable risk percentages can be executed for any set of data regardless of the underlying validity of assumed causal relationship between the agent and the disease. However, the results of those calculations have epidemiologic meaning only if the relationship between the agent and the disease is causal. The data presented in the Brownson study not only do not support a causal relationship between ETS and lung cancer but do not even indicate a positive statistical association between them. Because of these findings, the calculation of attributable risk percentages is not logically supported by the data upon which the calculations are based.

Further, the use of the phrase "attributable risk" is not universally accepted and a less assuming phrase is recommended:

> "For pedagogic reasons, language was occasionally used which seemed to imply the elimination of a particular risk factor would result in a measured reduction in incidence. This of course supposes that the association between risk factor and disease as estimated from the observational study is in fact a causal one. Unfortunately, the only way to be absolutely certain that a causal relationship exists is to intervene actively in the system by removing the disputed factor. In the absence of such evidence, a more cautious interpretation of the attributable risk measures would be in terms of the proportion of risk *explained* by the given factor, where 'explain' is used in the limited sense of statistical association." (Breslow and Day, 1980, pg 78; emphasis in the original)

With these caveats, estimates of the percentage of lung cancer cases among non-smoking women that are attributable to spousal smoking and workplace ETS are presented in this submission. These estimates are stratified by the type of interview of the case (direct vs surrogate) and by smoking status (lifetime never smoker vs former smoker). Unlike Alavanja's analyses, these

estimates do not dichotomize spousal smoking status but instead are based on the levels of exposure used in Brownson et al. (1992). The methods to calculate the attributable risk estimates and their standard deviations are based on an extension of the methods used by Alavanja et al. that were developed by Bruzzi et al. (1985) and Benichou and Gail (1990).

All statistical analyses were carried out using the statistical package SAS. The statistical analyses in the articles by Brownson and Alavanja are likely to have been executed using EPICURE, a less widely used package. Small differences (in the third decimal place) between some of the parameter estimates and confidence intervals calculated here and those presented by Brownson et al. (1992) may be attributed to the use of these different software packages. Small differences may also be attributable to differences in the specific age categories used to control confounding (Brownson et al. did not specify the cut-points used to define their four intervals) or to minor changes in the data set made before 1995 but after the analyses were executed for the 1992 publication.

RESULTS

The association between lung cancer and adult household ETS exposure is examined in Table 1 for all subjects and for lifetime never smokers. Exposure to ETS from all household smokers or from spousal smoking is examined using three exposure metrics: Never vs Ever, cigarette pack-years and cigarette pack-year hours/day.

The results presented in Table 1 duplicate almost exactly those presented in Table 2 of Brownson et al. (1992).[5] The patterns and magnitudes of association reported by Brownson et al. (1992) include:

* odds ratios of Never vs Ever exposure that range from 0.9 to 1.1, and none achieve statistical significance;

* odds ratios are always below 1.0 for the two intermediate exposure categories, and reach statistical significance for some combinations of exposure metric and type of subjects;

* no consistent increasing dose-response pattern for pack-years or pack-years x hours/day; and

* odds ratios of 1.2-1.3 for the highest exposure category, almost researching significance among the lifetime never smokers.

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[5] The caveat "almost" is present because of small differences in the third decimal place that result in differences in the first decimal place. For example, the upper confidence interval for the odds ratio between Never vs Ever exposure to household ETS from all household members is 1.3 in Table 1 compared to 1.2 in Table 2 of Brownson et al. (1992). The actual upper limit calculated here is 1.250 which would have rounded to 1.2 if it were 0.001 lower. This is the basis for the claim that small changes exist in the third decimal place.

The comparisons contained in Table 1 were executed separately for those with direct and surrogate interviews. These analyses are presented separately for lifetime never smokers (Table 2) and for former smokers (Tables 3a and 3b).

For lifetime never smokers who had direct interviews, the omnibus comparisons of "Never vs Ever" generate odds ratios of 1.0 and 0.9 for ETS exposure from all household members and from spouses, respectively. (Table 2) The odds ratios in the highest exposure categories are now either 1.0 or 1.1 and do not reach statistical significance or the magnitudes of 1.3 and 1.4 that were reported by Brownson et al. (1992) for all subjects. The magnitudes of the odds ratios in the intermediate categories now range between 0.7 and 1.1 and do not exhibit that abnormal pattern of consistently decreased risks that was reported by Brownson et al (1992) for all subjects.

The abnormal pattern of odds ratios that Brownson interpreted as "suggesting" an increased risk of lung cancer among the most heavily exposed lifetime never smokers is present only for those with surrogate interviews. (Table 2) Indeed, this pattern is present to an even more exaggerated degree. Specifically, the relative risks in the highest exposure categories now consistently reach 1.5, higher than the value of 1.3 reported by Brownson et al. for all subjects. The relative risk in the intermediate categories are again consistently below 1.0 but now reach even lower values of 0.5 and 0.6.

Because this pattern of risk appears only among lifetime never smoking cases with surrogate interviews, it is likely the result of the less valid data obtained from surrogate interviewees who do not have direct knowledge of the case's household ETS exposure. Further, because this pattern is observed only with the surrogate interviews, it should not be interpreted as being "suggestive" of a causal relationship between household ETS exposure and lung cancer.

Among former smokers, there is no pattern of increased risk of lung cancer associated with

household ETS exposure among those with direct or surrogate interviews. (Table 3a) For those with surrogate interviews, the odds ratios are all less than 1.0 indicating, if anything, a protective association between ETS exposure and lung cancer. For those with direct interviews, the odds ratios range between 0.7 and 1.1 for all exposure metrics and exposure categories except for two. These two odds ratios of 1.5 and 1.2 occur with the exposure metric for all household smokers.

However, these two slightly elevated odds ratios disappear when the confounding from the amount of former active smoking is removed. (Table 3b) Specifically, when the four-level categorization of active smoking is included in the logistic model, all the odds ratios range from 0.5 to 1.1, and there is no pattern of increased risk associated with household ETS exposure. The estimated odds ratios for the categories of former active smoking, though not all achieving statistical significance, are legitimate candidates to consider as confounders and do follow the anticipated pattern of association:

		Former Active Smoking		
Odds Ratio	95%CI	Intensity/ Duration		Time-Since-Quit
1.0	-	< 15 pack-years	and	> 25 years
1.3	(0.5,3.3)	< 15 pack-years	and	15 years ≤ < 25 years
			or	
		≥ 15 pack-years	and	> 25 years
2.5	(1.0, 6.0)	≥ 15 pack-years	and	15 years ≤ < 25 years
0.6	(0.2, 1.5)	Smoked >100 cigarettes but never smoked regularly for > 1 year or Smoked 0 < < 100 cigarettes in their lifetime		

The difference in the results between Tables 3a and 3b demonstrate that residual confounding can

be the source of odds ratios as large as 1.5. These differences also demonstrate the limitation of relying on epidemiologic measures of association as low as 1.5.

The Brownson data set recorded workplace ETS exposure in units of hours/day-years. (Brownson et al., 1992; Butler, 1994) Brownson et al. categorized subjects with workplace ETS exposure into quartiles of exposure. The amount of workplace ETS exposure experienced by subjects in each quartile is summarized in Table 4. For example, the average for the first (lowest) quartile is 7.2 hours/day-years. This amount of exposure could have been accumulated by someone having 7.2 hours/day of exposure for one year or by someone with 0.72 hours/day (43 minutes) of exposure for 10 years. The highest exposure quartile has an average 217.7 hours/day-years. This amount of exposure could have been accumulated by someone having 8 hours/day of exposure for approximately 27.2 years.

The association between lung cancer and workplace ETS exposure is examined separately for lifetime never smokers (Table 5a) and for former smokers (Table 5b). Two control groups are presented for each analysis: i) all women with no workplace ETS exposure, and ii) only women who have worked outside the home for at least six months and did not have workplace ETS exposure.

For lifetime never smokers with direct interviews, the omnibus comparisons of "Never vs Ever" generate odds ratios equal to 1.0 and 1.1 when the control group is all women and when the control group is restricted to women who worked outside the home, respectively. (Table 5a) These findings are consistent with Brownson et al. (1992, pg 1527) who stated "that there was no elevated lung cancer risk associated with passive smoke exposure in the workplace." For lifetime never smokers with surrogate interviews, the odds ratios for this omnibus comparison of Never vs Ever workplace ETS exposure are slightly lower than 1.0. (Table 5a). Again, this reenforces the conclusion that workplace ETS exposure is not associated with lung cancer risk among lifetime never smokers.

The dose-response pattern for lifetime never smokers who had direct interviews is approximately the same for the two controls groups: odds ratios are below 1.0 at the two lowest exposure categories, odds ratios are above 1.0 for the two highest exposure categories, and the highest odds ratio of 1.5-1.6 occurs not in the highest exposure group but in the penultimate exposure group. (Table 5a) The test for trend using either comparison group is not statistically significant (p-value = 0.47 for all women and = 0.29 women who worked outside the home). A similar trend is observed for cases with surrogate interviews when the comparison group is restricted to women who worked outside the home. (p-value for trend = 0.14) For surrogate interviews and the comparison group consisting of all women, all the odds ratios are less than or equal to 1.0. (p-value for trend = 0.83).

For surrogate interviews of lifetime never smokers, not having worked outside the home is associated with a significantly elevated odds ratio (= 2.7, 95% CI = 1.9, 3.9) for lung cancer. The higher risk in this group is the source of the higher odds ratios for workplace ETS exposure being observed for surrogate interviews when the comparison group is restricted women who had ever worked outside the home. Such extreme differences are not observed for direct interviews for whom not working outside the home is associated with a nonsignificant odds ratio (= 1.4, 95% CI = 0.9, 23). That is why, among direct interviews, the odds ratios for workplace ETS exposure are approximately the same for the two control groups. The difference between the direct and surrogate interviews in the odds ratios for lung cancer of never having worked outside the home (that is, 2.7 vs 1.4) is statistically significant. (p-value = 0.04) This suggests that the significant elevated risk among surrogate interviews of not having worked outside the home is most likely an artefact of the poor information obtained from surrogate interviews on occupation in general and workplace ETS in particular.

For former smokers with direct interviews, the omnibus comparisons of "Never vs Ever" generate odds ratios equal to 0.4 and 0.3 when the control group is all women and when the control group is restricted to women who worked outside the home, respectively. (Table 5b)

Both odds ratios are statistically significant, indicating the observed negative association between lung cancer and workplace ETS exposure is unlikely to be due to chance alone. A negative association of about this same magnitude is observed among former smokers with surrogate interviews. For both comparison groups and types of interview, decreased odds ratios of approximately the same magnitude are observed for each dose category. The absence of a dose-response pattern suggest that workplace ETS itself is not the source of the reduced risks of lung cancer.

The association of lung cancer risk with spousal and workplace ETS exposure is examined jointly in Table 6. The patterns of risk exhibited in the joint statistical analysis are approximately the same as those displayed when spousal smoking (Table 2 and 3b) and workplace ETS exposure (Table 5a and 5b) are examined without considering the other.

Specifically, for lifetime never smokers with direct interviews, the odds ratios for spousal smoking are approximately 1.0 for all exposure levels indicating no association and no dose-response relationship. The pattern of odds ratios observed with the less reliable surrogate interviews indicate elevated relative risks at the highest exposure categories. For workplace ETS exposure, the patterns are approximately the same for direct and surrogate interviews: relative risks below 1.0 for the two lowest exposure categories and relative risks above 1.0 at the two highest exposure.

For former smokers, workplace and spousal ETS exposure are associated with reduced risk of lung cancer. There is no strong dose-response trend for either direct or surrogate interviews.

The time-since-quit workplace and spousal ETS exposures are examined jointly in Table 7 for lifetime never smokers. For comparative purposes, the odds ratio estimated without controlling for time-since-quit (Table 6) are also presented. This time-since-quit analysis is not executed for former smokers due to the smaller sample size for this group.

Among those with a surrogate interview, the odds ratio for time-since-quit spousal smoking is 1.6, indicating that those whose spousal ETS exposure stopped at least 15 years ago are at higher risk than are those whose spousal ETS exposure was more recent. (Table 7) This is opposite to the pattern that is expected if the relationship between spousal ETS exposure and lung cancer were causal. Further, those with recent spousal ETS exposure do not display any association with intensity/ duration of exposure in that the odds ratios of 1.0, 0.4, 0.6 and 1.0 for the four dose groups do not show an elevation or dose-response pattern. All of the risk associated with intensity/ duration of spousal smoking is concentrated among those whose exposure stopped at least 15 years ago. (Table 7) This indicates that the *removal* of spousal ETS exposure is associated with a *greater* risk of lung cancer, a pattern that is not consistent with a causal relationship between ETS exposure and lung cancer.

For workplace ETS exposure, longer time-since-quit is associated with a nonsignificant increase in risk for those with direct interviews (odds ratio = 1.3) and for those with surrogate interview (odds ratio = 1.1). Again, this indicates that cessation of exposure is associated with an increase in risk, a pattern that is not consistent with a causal relationship between ETS exposure and lung cancer. Controlling for time-since-quit also generally reduces the magnitude of the odds ratio in each exposure group, indicating that the elevated risks occur to a greater degree in those whose workplace ETS exposure stopped $\geq$ 15 years ago.

An odds ratio less than 1.0 is observed for time-since-quit household ETS exposure for those with direct interviews. The odds ratio of 0.8 indicates that lower risk is observed among those whose exposure ceased at least 15 years ago. However, this measure of association is accompanied with a decreasing pattern of risk with greater intensity/ duration of exposure; that is, odds ratios equal 1.0, 1.5, 0.9 and 0.8 for the four dose categories. This simultaneous change in the pattern of risk is also not consistent with a causal relationship between spousal ETS exposure and lung cancer.

The estimates of the population attributable risk associated with spousal smoking status, workplace ETS exposure, former active smoking and previous lung disease are presented in Table 8. Estimates are provided by smoking status (lifetime never smokers and former smokers) and type of interview (direct and surrogate).

Spousal smoking status is associated with negative attributable risk for three of the four combinations of former smoking and type of interview. A negative attributable risk indicates a protection; that is, reduction in spousal smoking is associated with an *increase* in lung cancer cases. Clearly, this is not a basis to reduce the frequency of spousal ETS exposure. A positive attributable risk is observed only among lifetime never smokers who had a surrogate interview. As shown in Table 7, this elevated risk is concentrated among those whose exposure ceased more than 15 years ago and is not indicative of a causal relationship between ETS exposure and lung cancer.

Similarly, workplace ETS exposure is associated with negative attributable risk for three of the four combinations of former active smoking and type of interview. Among former smokers, the estimated negative attributable risks reach quite large values (-54.5% and -60.6%) and one is statistically significant. The only positive estimate of attributable risk is among lifetime never smokers with a direct interview. It was among these subjects, however, that higher risk was observed among those whose exposure ended more than 15 years ago, a pattern that is not consistent with a causal relationship between ETS exposure and lung cancer.

The estimated attributable risk for the combination of spousal and workplace ETS exposure is negative for former smokers regardless of their type of interview. The estimated attributable risks for former smokers are close to being statistically significant for both direct and surrogate interviews.

The estimated attributable risk for the combination of spousal and workplace ETS exposure is

positive for lifetime never smokers regardless of their type of interview. Each estimate is very close to zero and neither is statistically significant. Each positive estimate is the combination of one positive and one negative estimate for spousal and workplace ETS exposure, a pattern that is not consistent with a causal relationship.

DISCUSSION

The studies of Brownson et al. (1992) and Fontham et al. (1994) are the two largest epidemiologic studies of lung cancer and environmental tobacco smoke (ETS) in non-smokers. In its Notice of Proposed Rulemaking (NPR) on Indoor Air Quality, the Occupational Safety and Health Administration (OSHA) relied solely on the results of the study by Fontham et al. to the total exclusion of the study by Brownson et al. (OSHA, 1994, pg 15995) There is no scientific basis for this choice. Indeed, it is preferred to use the information from all the relevant epidemiologic studies. In its revision of the NPR, OSHA should expand its consideration of the scientific literature from the single study by Fontham et al. to all the epidemiologic studies. In such an evaluation, the results from the study by Brownson et al. should receive consideration and or weight at least as high as that given to the study by Fontham et al. (1991, 1994).

OSHA incorrectly reports that the Brownson study indicates a positive association between lung cancer and ETS exposure. (OSHA, 1994, pg 15993) The data and findings reported by Brownson et al. indicate that this is a ***negative*** study. Specifically, Brownson et al. (1992; pg 1526-1527) report that lung cancer risk was not associated with workplace ETS exposure or childhood ETS exposure. Brownson et al. also report that lung cancer risk was not associated with adult household and spousal ETS exposure when analyses were restricted to cases who had direct interviews.

Brownson et al. do not provide the results to document the finding of no association between

adult household ETS exposure and lung cancer among cases with direct interviews. Instead, Brownson et al. provided results of the analyses based on the combination of direct and surrogate interviews for cases. It is from this less reliable and less valid analysis that a slightly elevated risk of lung cancer (odds ratio = 1.3) was reported for those in the highest exposure group.

Because surrogate interviews are presumed to differ in quality from direct interviews (Rothman, 1986, pg 249), the results based in whole or in part on surrogate interviews should be discarded if they differ from those obtained from direct interviews alone. OSHA either did not recognize that the slight elevated risk was based on less reliable surrogate data or is not aware of the lower quality of surrogate data. Whatever the reason, in its revision of the preliminary quantitative risk assessment, OSHA should rely on the quantitative estimates of risk generated from direct interviews that are presented in this submission.

Analyses of these data by type of interview of the case are responsive to questions and comments from Dr. Steven Bayard of the USEPA regarding this author's previous submission (Butler, 1994) to OSHA on the Brownson study. Dr. Bayard also expressed concern regarding the validity of the data obtained from surrogates. (Bayard, 1995, pg 14722)

The analyses presented here support the statement from Brownson et al. (1992, pg 1526) that "(w)hen analyses were limited to direct interviews, no clear pattern of increase or decrease in risk estimates was apparent (for adult household and spousal ETS exposures)." (Tables 2 and 3b) The increased risk of lung cancer risk reported by Brownson et al. for those with $\geq$ 40 pack-years of exposure is isolated only among those with a surrogate interview, indicating that the elevated risk is an artefact of unreliable and invalid data obtained for these cases. This interpretation is strengthened by the observation that the increased risk among surrogate interviews is further isolated among those who ceased their exposure in the distant past ($\geq$ 15 years). Higher relative risk among those whose exposure ceased long along is not consistent with a causal relationship between ETS and lung cancer but is consistent with poorer quality recall of events that occurred

long ago.

Analyses of workplace ETS exposure by type of employer also indicate the absence of an association with lung cancer. (Table 5) The analyses provide additional evidence to support the finding of Brownson et al. (1992, pg 1527) of "no elevated lung cancer risk associated with passive smoke exposure in the workplace." Among lifetime never smokers, the two highest workplace ETS exposure groups have odds ratios greater than 1.0, the same as was reported previously by this author. (Butler, 1994) These odds ratios are not statistically significant and the test for trend is not statistically significant. (p-value for trend = 0.29) Further, the highest risks were found among those whose reported workplace ETS exposure occurred in the more distant past ($\geq$ 15 years ago), a pattern more consistent with recall bias than with a causal relationship between ETS and lung cancer.

Per this author's previous submission (Butler, 1994), analyses for workplace ETS exposure are presented using two different definitions of the unexposed groups. One analysis uses all subjects with no workplace ETS exposure, and the second analyses uses only subjects who have worked outside the home for at least six months and did not have workplace ETS exposure. The control groups differ in that the latter excludes women who did not work outside the home for six months or longer.

The previous submission by this author reported substantial differences in results between these two comparison groups that was the result of a substantial positive risk of lung cancer associated with having not worked outside the home. (Butler, 1994) This difference was present for lifetime never smokers but not for former smokers. (Butler, 1994, Tables 5 and 6) This counter-intuitive direction of risk is found in the analyses presented here to be an artefact of the type of interview of the case. A significant increase in risk (odds ratio = 2.7, 95% CI = 1.9, 3.9) was found only among those with a surrogate interview. The magnitude of association was much lower and not significant among those with direct interviews. This indicates that the difference

in risks connected with the use of different comparison groups is an artefact of the type of interview and not a reflection of a causal or a self-selection factor. This distortion could not have been identified in this author's previous submission to OSHA because NCI had not provided the data on the type of interview for the cases.

Dr. Bayard (1995, pg 14723) specifically commented on the pattern associated with the different comparison groups that was reported in this author's 1994 submission. He thought it relevant to OSHA's use of estimates of workplace risk from the study by Fontham et al. (1994):

> "It turns out that your risk estimates increase when you exclude those women who didn't work outside the home. The message here is to measure the effect of occupational ETS exposure (you must) restrict the analysis to subjects with a history of employment outside the home. This is something Fontham did not do. If you are going to take the Fontham measure, my suggestion to you is that measure has to be adjusted upward, either it has to be adjusted upward, that risk, or you have to ask Dr. Fontham to redo an analysis using only women exposed outside the home..."

The analyses presented here that control for type of interview and are restricted to "subjects with a history of employment outside the home" indicate no association between workplace ETS exposure and lung cancer. Thus, Dr. Bayard's recommendation that the risk estimates from the Fontham study be "adjusted upward" has no foundation. Indeed, the risk estimates from the Fontham study should be adjusted downward because they are consistent neither with the results of the Brownson study presented here nor with the combined analysis of all the epidemiologic studies of workplace ETS exposure. (LeVois and Layard, 1994)

These findings of a spurious positive bias due to less reliable surrogate interviews differ from those reported by Stockwell et al. (1992) who reported that surrogate interviews (other than with

spouse) were associated with a negative bias or dilution of an observed association. This apparent inconsistency between these two studies demonstrates the uncertainty of predicting the direction and magnitude of these types of bias. It also emphasizes the importance of conducting these types of analyses on each study of ETS and lung cancer that included both direct and surrogate interviews.

Because of the emphasis being placed upon the study by Fontham et al. (1991, 1994), it is essential that the raw data from this study be made available to OSHA and others to execute independent statistical and epidemiological examinations like those presented in this submission. The sharing of the data from Fontham et al. (1994) is consistent with the recommendation of the largest epidemiologic society in the United States: "when epidemiologic data are relevant to the governmental decision-making process, including public policy and regulatory decisions, investigators should share the data tapes and records as promptly and expeditiously as possible..." (Society for Epidemiologic Research, 1990) It is also consistent with NCI's policy of making data publicly available after NCI has published its planned analyses of them. Further, the National Research Council (1985, pg 27) recommends that "data relevant to public policy should be shared as quickly and as widely as possible." OSHA is encouraged to request these data from Fontham et al. and to make them available to all interested parties.

In summary, the results of these analyses provide additional background on the absence of an association between lung cancer and ETS as reported by Brownson et al. (1992). These data further elucidate the bias due to surrogate interviews that was the source of the slightly elevated risk reported for those in the highest household and spousal ETS exposure categories. These data also provide further support for the finding of Brownson et al. (1992) on an absence of an association between workplace ETS exposure and lung cancer. In its revised NPR, OSHA should give substantial consideration and weight to these findings from one of the two largest epidemiologic studies of ETS and lung cancer.

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TABLES

Table 1. Adjusted Odds Ratios (OR[a]) and 95% Confidence Intervals (CI) for the Association Between ETS Exposure During Adulthood and Lung Cancer, The Brownson Study.

Source of Exposure	All Subjects[b]				Lifetime Nonsmokers			
	# Cases	# Controls	OR	95% CI	# Cases	# Controls	OR	95% CI
All household members								
Never	221	527	1.0	-	170	470	1.0	-
Ever	394	873	1.0	0.8, 1.3	261	696	1.1	0.8, 1.3
Cigarette pack-years								
0	221	527	1.0	-	170	470	1.0	-
0< <15	88	234	0.9	0.6, 1.1	56	181	0.9	0.6, 1.3
15≤ <40	91	261	0.8	0.6, 1.1	62	199	0.9	0.6, 1.2
40≤	146	264	1.3	1.0, 1.6	107	217	1.4	1.0, 1.8
Cigarette pack-years x hours/day[c]								
0	221	527	1.0	-	170	470	1.0	-
0< <50	90	261	0.8	0.6, 1.1	63	206	0.9	0.6, 1.2
50≤ ≤175	89	246	0.8	0.6, 1.1	58	189	0.9	0.6, 1.2
175<	124	238	1.2	0.9, 1.6	92	192	1.3	1.0, 1.8
Spouses only								
Never	287	650	1.0	-	213	568	1.0	-
Ever	328	750	0.9	0.8, 1.1	218	598	1.0	0.8, 1.2
Cigarette pack-years								
0	287	650	1.0	-	213	568	1.0	-
<0 <15	58	166	0.7	0.5, 1.0	32	128	0.7	0.5, 1.0
15≤ <40	81	258	0.7	0.5, 0.9	54	200	0.7	0.5, 1.0
40≤	150	266	1.2	1.0, 1.6	110	216	1.3	1.0, 1.8
Cigarette pack-years x hours/day[c]								
0	287	650	1.0	-	213	568	1.0	-
0< <50	64	201	0.7	0.5, 0.9	41	161	0.7	0.5, 1.0
50≤ ≤175	81	237	0.7	0.5, 1.0	52	183	0.8	0.5, 1.1
175<	126	241	1.2	0.9, 1.5	94	193	1.3	1.0, 1.7

[a] Adjusted for age, history of previous lung disease, and active smoking (never vs. fomer; all subjects).
[b] Includes lifetime nonsmokers and ex-smokers who had stopped at least 15 years before diagnosis or who had smoked for less than 1 pack-year.
[c] The product of total pack-years and average number of hours exposed per day to passive smoke in the home.

Table 2. **Adjusted Odds Ratios (OR[a]) and 95% Confidence Intervals for the Association Between Spousal Smoking Status and Lung Cancer in Lifetime Never Smoking Women, by Type of Interview, The Brownson Study.**

Source of Exposure	Type of Interview: Direct # Cases	Direct # Controls	Direct OR	Direct 95% CI	Surrogate # Cases	Surrogate # Controls	Surrogate OR	Surrogate 95% CI
All household members								
Never	61	470	1.0		109	470	1.0	
Ever	93	696	1.0	0.7, 1.4	168	696	1.1	0.8, 1.4
Cigarette pack-years								
0	61	470	1.0		109	470	1.0	
0< <15	27	181	1.1	0.7, 1.9	29	181	0.7	0.5, 1.2
15≤ <40	24	199	0.9	0.6, 1.5	38	199	0.8	0.6, 1.3
40≤	30	217	1.0	0.6, 1.6	77	217	1.5	1.1, 2.2
Cigarette pack-years x hours/day[b]								
0	61	470	1.0		109	470	1.0	
0< <50	28	206	1.0	0.6, 1.7	35	206	0.8	0.5, 1.2
50≤ ≤175	19	189	0.8	0.4, 1.3	39	189	0.9	0.6, 1.4
175<	29	192	1.1	0.7, 1.8	63	192	1.5	1.0, 2.1
Spouses only								
Never	80	568	1.0		133	568	1.0	
Ever	74	598	0.9	0.6, 1.2	144	598	1.0	0.8, 1.4
Cigarette pack-years								
0	80	568	1.0		133	568	1.0	
0< <15	18	128	1.0	0.6, 1.7	14	128	0.5	0.3, 0.9
15≤ <40	20	200	0.7	0.4, 1.2	34	200	0.7	0.5, 1.1
40 ≤	32	216	1.0	0.6, 1.6	78	216	1.5	1.1, 2.1
Cigarette pack-years x hours/day[b]								
0	80	568	1.0		133	568	1.0	
0< <50	18	161	0.8	0.5, 1.4	23	161	0.6	0.4, 1.0
50≤ ≤175	17	183	0.7	0.4, 1.1	35	183	0.8	0.5, 1.2
175<	30	193	1.1	0.7, 1.7	64	193	1.5	1.0, 2.0

[a] Adjusted for age and history of previous lung disease.
[b] The product of total pack-years and average number of hours exposed per day to passive smoke in the home.

Table 3a. Adjusted Odds Ratios (OR[a]) and 95% Confidence Intervals for the Association Between Spousal Smoking Status and Lung Cancer in Women who are Former Smokers, by Type of Interview, The Brownson Study.

Source of Exposure	Type of Interview: Direct # Cases	Direct # Controls	Direct OR	Direct 95% CI	Surrogate # Cases	Surrogate # Controls	Surrogate OR	Surrogate 95% CI
All household members								
Never	14	57	1.0		37	57	1.0	
Ever	54	177	1.2	0.6, 2.4	79	177	0.7	0.4, 1.2
Cigarette pack-years								
0	14	57	1.0		37	57	1.0	
0< <15	13	53	1.0	0.4, 2.3	19	53	0.6	0.3, 1.1
15≤ <40	11	62	0.7	0.3, 1.8	18	62	0.5	0.2, 1.0
40≤	17	47	1.5	0.6, 3.3	22	47	0.7	0.4, 1.4
Cigarette pack-years x hours/day[b]								
0	14	57	1.0		37	57	1.0	
0< <50	12	55	0.9	0.4, 2.1	15	55	0.4	0.2, 0.9
50≤ ≤175	13	57	0.9	0.4, 2.1	18	57	0.5	0.3, 1.0
175<	12	46	1.1	0.5, 2.7	20	46	0.7	0.4, 1.4
Spouses only								
Never	24	82	1.0		50	82	1.0	
Ever	44	152	1.0	0.5, 1.7	66	152	0.7	0.5, 1.2
Cigarette pack-years								
0	24	82	1.0		50	82	1.0	
0< <15	11	38	1.0	0.4, 2.3	15	38	0.7	0.3, 1.3
15≤ <40	10	58	0.6	0.2, 1.3	17	58	0.5	0.3, 1.0
40≤	17	50	1.1	0.5, 2.3	23	50	0.8	0.4, 1.4
Cigarette pack-years x hours/day[b]								
0	24	82	1.0		50	82	1.0	
0< <50	11	40	0.9	0.4, 2.1	12	40	0.5	0.2, 1.0
50≤ ≤175	11	54	0.7	.03, 1.5	18	54	0.6	0.3, 1.1
175 <	12	48	0.9	0.4, 1.9	20	48	0.7	0.4, 1.3

[a] Adjusted for age and history of previous lung disease.
[b] The product of total pack-years and average number of hours exposed per day to passive smoke in the home.

Table 3b. **Adjusted Odds Ratios (OR[a]) and 95% Confidence Interval for the Association Between Spousal Smoking and Lung Cancer in Women who are Former Smokers, Controlling for Former Smoking Intensity and Time Since Quit, by Type of Interview, The Brownson Study.**

	Type of Interview							
	Direct Interview				Surrogate Interview			
	# Cases	# Controls	OR	95% CI	# Cases	# Controls	OR	95% CI
All household members								
Never	14	55	1.0		20	55	1.0	
Ever	51	173	1.1	0.5, 2.1	55	173	0.8	0.4, 1.4
Cigarette pack-years								
0	14	55	1.0		20	55	1.0	
0< <15	13	53	1.0	0.4, 2.4	15	53	0.7	0.3, 1.7
15≤ <40	11	59	0.6	0.3, 1.6	12	59	0.5	0.2, 1.1
40≤	15	46	1.0	0.4, 2.4	13	46	0.6	0.2, 1.4
Cigarette pack-years x hours/day[b]								
0	14	55	1.0		20	55	1.0	
0< <50	12	55	0.8	0.3, 2.0	12	55	0.6	0.2, 1.4
50≤ ≤175	12	55	0.7	0.3, 1.7	12	55	0.5	0.2, 1.1
175<	12	44	0.9	0.4, 2.2	13	44	0.7	0.3, 1.6
Spouses only								
Never	23	80	1.0		30	80	1.0	
Ever	42	148	0.8	0.4, 1.5	45	148	0.7	0.4, 1.2
Cigarette pack-years								
0	23	80	1.0		30	80	1.0	
0< <15	11	38	0.9	0.4, 2.1	12	38	0.8	0.3, 1.8
15≤ <40	10	55	0.5	0.2, 1.2	9	55	0.3	0.1, 0.8
40≤	15	49	0.8	0.3, 1.7	16	49	0.6	0.3, 1.3
Cigarette pack-years x hours/day[b]								
0	23	80	1.0		30	80	1.0	
0< <50	11	40	0.8	0.3, 1.8	9	40	0.5	0.2, 1.2
50≤ ≤175	10	52	0.5	0.2, 1.2	13	52	0.5	0.2, 1.2
175≤	12	46	0.7	0.3, 1.6	13	46	0.6	0.3, 1.3

[a] Adjusted for age, history of previous lung disease and active smoking (4 levels, see text).
[b] The product of total pack-years and average number of hours expected per day to passive smoke in the home.

Table 4.
Quartiles Of Hours/Day-Years Exposure to ETS in the Workplace for Cases and Controls, The Brownson Study

	Quartiles, Hours/Day-Years Exposure to ETS in the Workplace			
Variable	Lowest	2	3	Highest
Number of Subjects	178	183	178	167
Hours/Day-Years				
Mean	7.2	27.2	81.2	217.7
Median	7.5	26	80	200
Maximum	15	40	120	504
Minimum	0.5	16	41	125

Table 5a.
Adjusted Odds Ratios (OR*) and 95% Confidence Intervals (CI) for the Association Between Workplace ETS Exposure and Lung Cancer, by Type of Interview, The Brownson Study.

Lifetime Never Smokers

Source of Exposure	Type of Interview: Direct # Cases	Direct # Controls	Direct OR	Direct 95% CI	Surrogate # Cases	Surrogate # Controls	Surrogate OR	Surrogate 95% CI
All Women								
Workplace ETS								
Never	91	709	1.0		146	709	1.0	
Ever	59	434	1.0	0.7, 1.5	56	434	0.7	0.5, 0.9
Hours/Day-Years								
0	91	709	1.0		146	709	1.0	
Lowest	12	118	0.8	0.4, 1.5	10	118	0.4	0.2, 0.9
2	12	115	0.8	0.4, 1.5	9	115	0.4	0.2, 0.8
3	21	103	1.5	0.9, 2.5	18	103	0.9	0.5, 1.5
Highest	14	98	1.1	0.6, 2.0	19	98	1.0	0.6 1.7
Women Who Worked Outside the Home								
Workplace ETS								
Never	66	560	1.0		85	560	1.0	
Ever	59	434	1.1	0.8, 1.7	56	434	0.9	0.6, 1.3
Hours/Days-Years								
0	66	560	1.0		85	560	1.0	
Lowest	12	118	0.8	0.4, 1.6	10	118	0.6	0.3, 1.2
2	12	115	0.9	0.4, 1.7	9	115	0.5	0.3, 1.1
3	21	103	1.6	0.9, 2.9	18	103	1.2	0.7, 2.1
Highest	14	98	1.2	0.6, 2.2	19	98	1.3	0.7, 2.3

* Adjusted for age and history of previous lung disease.

Table 5b.
Adjusted Odds Ratio (OR*) and 95% Confidence Intervals (CI) for the Association Between Workplace ETS Exposure and Lung Cancer, by Type of Interview, The Brownson Study

Former Smokers

Source of Exposure	Type of Interview: Direct # Cases	Direct # Controls	Direct OR	Direct 95% CI	Surrogate # Cases	Surrogate # Controls	Surrogate OR	Surrogate 95% CI
All Women								
Workplace ETS								
Never	42	110	1.0		32	110	1.0	
Ever	21	115	0.4	0.2, 0.8	21	115	0.4	0.2, 0.8
Hours/Day-Years								
0	42	110	1.0		32	110	1.0	
Lowest	3	30	0.3	0.1, 0.9	5	30	0.4	0.1, 1.4
2	7	34	0.5	0.2, 1.2	6	34	0.4	0.1, 1.1
3	6	27	0.5	0.2, 1.3	3	27	0.3	0.1, 1.1
Highest	5	24	0.4	0.1, 1.2	7	24	0.5	0.2, 1.6
Women Who Worked Outside the Home								
Workplace ETS								
Never	38	90	1.0		18	90	1.0	
Ever	21	115	0.3	0.2, 0.6	21	115	0.5	0.2, 1.1
Hours/Days-Years								
0	38	90	1.0		18	90	1.0	
Lowest	3	30	0.2	0.1, 0.8	5	30	0.5	0.1, 1.8
2	7	34	0.4	0.1, 1.0	6	34	0.4	0.1, 1.4
3	6	27	0.4	0.1, 1.1	3	27	0.3	0.1, 1.4
Highest	5	24	0.3	0.1, 1.0	7	24	0.7	0.2, 2.2

* Adjusted for age, history of previous lung disease and active smoking (4 levels; see text)

Table 6.
Adjusted Odds Ratios (OR*) and 95% Confidence Intervals for the Association of Lung Cancer with Spousal Smoking and Workplace ETS Exposure, by Smoking Status and Type of Interview, The Brownson Study

	Smoking Status							
	Lifetime Never Smoker				Former Smoker			
	Direct Interview		Surrogate Interview		Direct Interview		Surrogate Interview	
Variable	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Spousal Smoking (pack years)								
0	1.0	-	1.0	-	1.0	-	1.0	
0 < <15	1.1	0.6, 1.9	0.6	0.3, 1.2	1.0	0.4, 2.4	0.6	0.2, 2.0
15≤ <40	0.8	0.5, 1.4	1.2	0.7, 2.0	0.7	0.3, 1.8	0.4	0.1, 1.3
40 ≤	1.0	0.6, 1.6	1.6	1.1, 2.6	0.7	0.3, 1.7	0.5	0.2, 1.5
Workplace ETS (Quartiles)								
0	1.0	-	1.0	-	1.0	-	1.0	
Lowest	0.9	0.4, 1.7	0.6	0.3, 1.1	0.3	0.1, 0.9	0.5	0.1, 1.9
2	0.8	0.4, 1.7	0.5	0.2, 1.1	0.5	0.2, 1.3	0.4	0.1, 1.3
3	1.7	1.0, 2.9	1.3	0.7, 2.3	0.5	0.2, 1.4	0.4	0.1, 1.6
Highest	1.3	0.7, 2.4	1.3	0.7, 2.2	0.4	0.1, 1.2	0.5	0.2, 1.9

* Adjusted for age, history of previous lung disease and active smoking (4 levels, see text).

Table 7.
Adjusted Odds Ratios (OR) and 95% Confidence Intervals for the Association of Lung Cancer with Spousal Smoking and Workplace ETS Exposure, by Smoking Status and Type of Interview, The Brownson Study

Lifetime Never Smokers

	Type of Interview							
	Direct				Surrogate			
	Model 1		Model 2		Model 1		Model 2	
Variable	OR*	95%CI	OR**	95% CI	OR*	95% CI	OR**	95% CI
Spousal Smoking (pack years)								
0	1.0	-	1.0	-	1.0	-	1.0	-
0 < <15	1.1	0.6, 1.9	1.5	0.5, 4.3	0.6	0.3, 1.2	0.4	0.1, 1.3
15≤ <40	0.8	0.5, 1.4	0.9	0.4, 2.2	1.2	0.7, 2.0	0.6	0.2, 1.5
40 ≤	1.0	0.6, 1.6	0.8	0.4, 1.7	1.6	1.1, 2.6	1.0	0.5, 2.0
Spousal Time Since Quit								
0< <15			1.0	-			1.0	-
15 ≤			0.8	0.3, 1.9			1.6	0.7, 3.8
Workplace ETS (Quartiles)								
0	1.0	-	1.0	-	1.0	-	1.0	-
Lowest	0.9	0.4, 1.7	0.7	0.3, 1.7	0.6	0.3, 1.1	0.4	0.1, 1.3
2	0.8	0.4, 1.7	0.7	0.3, 1.9	0.5	0.2, 1.1	0.5	0.2, 1.6
3	1.7	1.0, 2.9	1.3	0.6, 2.9	1.3	0.7, 2.3	0.9	0.4, 2.2
Highest	1.3	0.7, 2.4	1.3	0.6, 2.9	1.3	0.7, 2.2	1.3	0.6, 2.8
Workplace Time Since Quit								
0< <15			1.0	-			1.0	-
15 ≤			1.3	0.6, 2.9			1.1	0.4, 2.6

* Adjusted for age, history of previous lung disease, spousal smoking (4 levels) and workplace ETS (5 levels).

** Adjusted for age, history of previous lung disease, spousal smoking (4 levels), time-since-quit spousal smoking, workplace ETS (5 levels) time-since-quit ETS.

Table 8.
Adjusted Odds Ratios (OR*) and Population Attributable Risks for Lung Cancer, by Smoking Status and Type of Interview, The Brownson Study

	Lifetime Never Smoker				Former Smoker			
	Direct Interview		Surrogate Interview		Direct Interview		Surrogate Interview	
Risk Factor	OR*	Attrib. Risk	OR*	Attrib. Risk	OR*	Attrib. Risk	OR*	Attrib. Risk
Spousal Smoking (pack years)								
0	1.0		1.0		1.0		1.0	
0 < <15	1.1	-3.2	0.6	10.3	1.0	-18.9	0.6	-52.7
15≤ <40	0.8	(-22.4, 15.9)	1.2	(-7.5, 28.2)	0.7	(-72.3, 34.6)	0.4	(-133.0, 27.2)
40 ≤	1.0		1.6		0.7		0.5	
Workplace ETS (Hours/Day-Years)								
0	1.0		1.0		1.0		1.0	
Lowest	0.9	5.4	0.6	-6.7	0.3	-54.4	0.5	-60.6
2	0.8	(-12.4, 23.2)	0.5	(-24.1, 10.8)	0.5	(-104, -4.6)	0.4	(-141.0, 19.7)
3	1.7		1.3		0.5		0.4	
Highest	1.3		1.3		0.4		0.5	
Spousal Smoking & Workplace ETS		2.6		4.8		-90.2		-141.2
		(-23.1, 28.4)		(-20.0, 29.7)		(-202, 21.4)		(-324, 41.2)
Previous Lung Disease								
No	1.0	9.5	1.0	-3.8	1.0	11.6	1.0	6.4
Yes	1.3	(-5.1, 24.2)	0.9	(-18.1, 10.5)	1.3	(-17.5, 40.7)	1.2	(-28.1, 41.0)
Active Smoking								
None					1.0		1.0	
Level 1					1.9	16.2	0.8	5.6
2					2.4	(7.1, 25.2)	0.9	(-2.5, 13.8)
3					3.7		5.1	
4					1.1		0.4	

* Adjusted for spousal smoking status, workplace ETS exposure, age, previous lung disease and active smoking (4 levels, see text)

ENVIRONMENTAL
RISK ANALYSIS

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Re-Analysis of Data Provided in Fontham et al. (1994):

No Increase in the Risk of Lung Cancer Associated With Adult ETS Exposure

Comments to:
Docket Office, Docket No. H-122 Room N-2625
U.S. Department of Labor
200 Constitution Ave., NW
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TABLE OF CONTENTS

EXECUTIVE SUMMARY

> "Since few members of the clinical or biomedical research community are conversant in the use and interpretation of biostatistics, most readers assume that when an article appears in a journal, the reviewers and editors have scrutinized every aspect of the manuscript, including the use of statistics. Unfortunately, this is not so."
>
> Stanton Glantz, *Primer on Biostatistics*, 1992, p. 7

During the public hearings, OSHA staff repeatedly asked witnesses to provide data that demonstrate the specific sources and magnitudes of bias claimed to be present in the study by Fontham et al. (1991 [Ex. 8-106], 1994 [Ex. 377]). This submission provides analyses that demonstrate and quantify the presence of such a study bias. This bias explains completely the crude association between adult ETS exposure and lung cancer that was reported by Fontham et al. (1994 [Ex. 377]).

The Fontham study was specifically designed to assess the association of lung cancer with childhood and adult ETS exposure. The data provided by Fontham et al. (1994 [Ex. 377], Table 8) on this joint exposure are re-analyzed and are found to demonstrate the bias in this study. In this re-analysis, never-smoking women with neither childhood nor adult exposure to ETS are used as the 'baseline' or 'comparison' group for all other combinations of exposure. This is a standard practice for epidemiological research but was not the approach presented by Fontham et al. (1994 [Ex. 377]).

As shown in the table below, never-smoking women with both childhood and adult ETS exposure are at no greater risk of lung cancer than never-smoking women with neither exposure.[1] Never-smoking women with adult ETS exposure (regardless of their childhood ETS exposure) are at no increased risk for lung cancer, relative to women with neither childhood nor adult ETS exposure.

[1] The data in the table refer to self-respondents. Similar patterns of association are observed for all respondents (self- and proxy-).

Crude Odds Ratios for Lung Cancer Risk			
		Childhood ETS Exposure	
		No	Yes
Adult ETS Exposure	No	1.00 (Baseline)	0.35 (0.12, 0.99)
	Yes	1.00 (0.60, 1.67)	1.00 (0.61, 1.64)

Because adult ETS exposure (which includes workplace ETS exposure) is not associated with an increased risk of lung cancer, OSHA cannot rely on this study to support its proposed regulation of ETS in the workplace. Whether relying only on Fontham et al. (1994 [Ex. 377]) or on the combined analyses of all relevant epidemiological studies, OSHA should conclude that adult ETS exposure is not associated with an increased risk of lung cancer.

In the table shown above, never-smoking women with childhood but no adult ETS exposure are at a significantly ***lower*** risk of lung cancer compared to never-smoking women with neither exposure. This statistically significant negative association is most likely an artifact of bias either in study design or data collection. This bias is also the source of artificially inflated statistical estimates that incorrectly indicate a positive association between adult ETS exposure and lung cancer. This is the specific information called for by OSHA that demonstrates and quantifies the presence of bias in this study. This is exactly the type of evidence that OSHA has implied is required for a re-evaluation of its position that the results of Fontham et al. (1994 [Ex. 377]) provide reliable evidence of a positive association between adult ETS exposure and lung cancer.

Fontham et al. (1994 [Ex. 377]) do not present the measures of association in the above table. Instead, Fontham et al. (1994 [Ex. 377], Table 8) present an analysis based on the stratum-specific odds ratios for adult ETS exposure among never-smoking women with childhood ETS exposure (that is, 2.86 = 1.00/ 0.35) and among never-smoking women without childhood ETS exposure (that is, 1.00). To properly interpret the stratum-specific OR = 2.86, it is necessary to know that the never-smoking women with childhood but no adult ETS exposure are at a significantly ***lower*** risk of lung cancer compared to never-smoking women with neither

childhood nor adult ETS exposure. This essential feature of the data is not mentioned by Fontham et al. (1994 [Ex. 377]). Fontham et al.'s failure to mention this fact makes their analysis incomplete and their interpretation misleading.

The presentation of results in Fontham et al. (1994 [Ex. 377]) has misled other researchers (Bayard, 1995) to believe that adult ETS exposure preceded by childhood ETS exposure is associated with an even greater risk of lung cancer. This is not indicated by the data. As shown in the above table, those with adult ETS exposure are not at an increased risk of lung cancer, regardless of their childhood ETS exposure. The data of Fontham et al. (1994 [Ex. 377]) indicate adult ETS exposure is not associated with an increased risk of lung cancer (OR = 1.00, 95% CI 0.62, 1.63), regardless of whether or not the subject had childhood ETS exposure.

Influences directed to the identification and reporting of an association between ETS and lung cancer may have affected the reporting of the results in Fontham et al. (1994 [Ex. 377]). The reporting of results in the study by Brownson et al. (1992 [Ex. 8-36]), the other major case-control study of lung cancer and ETS exposure, may have been affected in a similar way. (Butler, 1995 [Ex. 454]) Because of the apparent tendency to "shade" the findings of scientific research away from the acknowledgment of the absence of an association between ETS exposure and lung cancer, OSHA should not rely upon the published results to provide a complete report of the information contained in each study. OSHA should obtain the raw data for all such studies and then make these data available to the public for confirmatory analyses.

INTRODUCTION

In its proposed rulemaking, the Occupational Safety and Health Administration (OSHA) considered the alleged risk of lung cancer associated with exposure to environmental tobacco smoke (ETS). (OSHA, 1994 [Ex. 7]) OSHA has identified approximately 34 epidemiological studies on lung cancer and ETS exposure. (Brown, 1995 [Ex. 340-1787]) When considered as a whole, these studies do not demonstrate a causal relationship between lung cancer and ETS exposure. (Lee, 1992 [Ex. 454], Chapter 3; Layard, 1994 [Ex. 9-47603]) The summary measure of association between spousal smoking status and lung cancer calculated from U.S. studies does not achieve statistical significance and is too small to be considered scientifically reliable. (Layard, 1994 [Ex. 9-47603]) The summary measure of the association between workplace ETS exposure and lung cancer also does not achieve statistical significance and is even smaller and less reliable. (LeVois and Layard, 1994)

In its assessment of the magnitude of the epidemiological association between workplace ETS exposure and lung cancer, OSHA has incorrectly disregarded the data from the other relevant epidemiological studies in favor of the results from the single epidemiological study by Fontham et al. 1991 [Ex. 8-106]).[2] Specifically, in its proposed rulemaking, OSHA uses the estimated association of OR = 1.34 reported by Fontham et al. (1991 [Ex. 8-106], Table 6) between lung cancer and workplace ETS exposure. In general, it is incorrect to evaluate a scientific hypothesis with the data from only one study when the available epidemiological literature is as large as that for ETS and lung cancer. OSHA's choice is especially egregious because the single study it relied upon reports an association that is inconsistent with the combined results from all the studies.

Associations as small as that reported by Fontham et al. (1991 [Ex. 8-106]) for ETS exposure can result from numerous sources of bias in study design, data collection or data analysis. For this reason, epidemiologists typically discount and do not rely upon such small associations. However, this standard epidemiological treatment of small magnitudes of association has been

[2] The results in Fontham et al. (1991 [Ex. 8-106]) have been updated in Fontham et al. (1994 [Ex. 377]). The results in Fontham et al. (1994 [Ex. 377]) are, in general, similar to those in Fontham et al. (1991 [Ex. 8-106]).

ignored by OSHA (1994 [Ex. 7]) and USEPA (1992 [Ex. 8-311]) in their consideration of the epidemiological studies of ETS.

OSHA staff repeatedly asked witnesses to provide data that demonstrate the specific sources and magnitudes of bias in the Fontham study. In the absence of such specific data and demonstrations, OSHA implied that it will not concede the potential influence of such biases which, on the basis of general epidemiological practice and experience, are expected to be present to some degree.

This submission re-examines the results presented in Fontham et al. (1994 [Ex. 377]) and provides analyses that demonstrate and quantify the presence of a study bias. This is the type of evidence that OSHA implied was required to initiate a re-evaluation of its position that the results of Fontham et al. (1994 [Ex. 377]) provide reliable evidence of a positive association between adult ETS exposure and lung cancer. The bias identified in these analyses explains completely the crude association between adult ETS exposure and lung cancer that was reported by Fontham et al. (1994 [Ex. 377]). Based on available information, this bias is also expected to explain the reported association between lung cancer risk and workplace ETS exposure.

OSHA's preliminary quantitative risk assessment for workplace ETS and lung cancer includes estimates of risk obtained solely from the Fontham study. Mr. Martonik, testifying on behalf of OSHA, was asked during the public hearings whether OSHA's policy is to obtain the raw data for the studies in the record. Mr. Martonik (tr. 65) replied that "(i)t depends upon the study and its relevance towards making our finding of significant risk." Because OSHA's significant risk analysis of lung cancer relies heavily on the results from the Fontham study which have been shown here to be biased towards the overestimation, OSHA should insist on obtaining the raw data from the Fontham study. These data should also be made public so that others could execute confirmatory analyses.

The opportunity to document the presence of bias in the Fontham study is restricted by the limited and selected information contained in the published articles from the study. Additional documentation for the study bias presented in this submission is possible only if the raw data for the Fontham study are made available for more detailed statistical analyses.

RE-ANALYSIS OF DATA CONTAINED IN FONTHAM ET AL. (1994 [EX. 377])

Background

Because of OSHA's familiarity with the Fontham study, extensive background information on its design, execution, analysis and reported findings is not repeated here.

Fontham et al. (1994 [Ex. 377]) collected data using "an extensive structured questionnaire designed to obtain information on household, occupational and other exposures to ETS during each study subject's *lifetime*...". (Fontham et al., 1994 [Ex. 377], p. 1753, emphasis added) Because the study was specifically designed to collect information on ETS exposure during the subject's adulthood and childhood, these data must be analyzed to assess the joint impact of these two ETS exposures.

Fontham et al. (1994 [Ex. 377]; Table 8) provide information on the joint exposure to childhood ETS exposure and to adult ETS exposure. The joint exposure to these two measures of ETS are the basis for the analyses presented here. Childhood ETS exposure refers to whether a smoker was a member of the subject's childhood household. Adult ETS exposure refers to ETS exposure at the home, workplace or social settings during adulthood. Fontham et al. (1994 [Ex. 377]) do not provide the data to examine the joint exposure to childhood ETS with each of the individual sources of adult ETS exposure.

The joint statistical analysis is first presented with childhood and adult ETS exposure measured as "Yes vs No." The joint statistical analysis is then presented using the four dose levels for adult ETS exposure defined by Fontham et al. (1994 [Ex. 377], Table 8). Dose levels for childhood ETS exposure for the joint analysis were not provided by Fontham et al. (1994 [Ex. 377]) and, thus, cannot be included in the statistical analyses presented here.

The joint statistical analyses for childhood and adult ETS exposure will focus on the data for self-respondents because the data for this group are expected to have a higher degree of validity than the data for the proxy-respondents, particularly for childhood ETS exposure. The same analyses are also executed for all respondents (self- and proxy-respondents). The same general patterns observed for self-respondents are also observed for all respondents. Analyses are

presented for all lung cancer types. Fontham et al. (1994 [Ex. 377]) did not present the data to execute these analyses on subgroups of types of lung cancers.

Statistical Methods

Only crude odds ratios (ORs) are presented because the data are not available to calculate adjusted ORs. The adjusted and crude ORs presented by Fontham et al. (1994 [Ex. 377]) differ only slightly. Because of that similarity, the pattern displayed by the crude ORs presented in this submission is also expected to hold for the adjusted ORs.

In the analysis of the risk associated with joint exposure to two factors, it is the standard practice in epidemiological research to define the baseline group to be those with exposure to neither factor. (Breslow and Day, 1980, p. 195-200; Kleinbaum, Kupper and Morgenstern, 1982, p. 407-412, 414-415, 424; Schlesselman, 1982, p. 66, 196-200, Rothman, 1986, p. 321).[3] This baseline group, by definition, has an odds ratio equal to 1.00. As shown in the table below, the OR_{01} measures the risk associated with childhood but no adult ETS exposure; the OR_{10} measures the risk associated with adult but no childhood ETS exposure; and the OR_{11} measures the risk associated with exposure to both childhood and adult ETS exposure.[4]

		Childhood ETS Exposure	
		No	Yes
Adult ETS Exposure	No	1.00 (Baseline)	OR_{01}
	Yes	OR_{10}	OR_{11}

[3] The texts by Kleinbaum, Kupper and Morgenstern (1982) and Schlesselman (1982) were cited in Fontham et al. (1994 [Ex. 377], p. 1754) as the authoritative sources for the logistic regression analyses used "to estimate summary adjusted ORs."

[4] In this notation, the 1's and 0's as subscripts indicate the presence or absence of the exposure. The order of the subscripts is informative. The first subscript refers to adult ETS exposure (the row factor) and the second subscript refers to childhood ETS exposure (the column factor).

It is also standard epidemiological practice to calculate stratum-specific odds ratios for one of the factors conditional on each level of the second factor. Stratum-specific odds ratios for adult ETS exposure (defined for each level of childhood ETS exposure) are defined as follows:

		Childhood ETS Exposure: No		Childhood ETS Exposure: Yes	
		No	Yes	No	Yes
Adult ETS Exposure	No	1.00 (Baseline)		1.00 (Baseline)	
	Yes	$OR_{1(0)}=OR_{10}/1.00$		$OR_{1(1)}=OR_{11}/OR_{01}$	

By definition, $OR_{1(0)}=OR_{10}$.[5] However, $OR_{1(1)}$ and OR_{11} have very different definitions, and it is incorrect to interpret them in the same manner. Specifically, when $OR_{1(1)} > 1$, it is not clear that this is due to $OR_{11} > 1.00$ or due to $OR_{01} < 1.00$.

Fontham et al. (1994 [Ex. 377], Table 8) presents only stratum-specific odds ratios. As is shown below, failure to recognize or to clearly present the difference between the stratum-specific odds ratios (that is, $OR_{1(1)}$) and OR_{11} is the source of the misleading interpretation of results by Fontham et al. (1994 [Ex. 377]).

It is also standard epidemiological practice to assess whether $OR_{1(0)}$ and $OR_{1(1)}$ are equal. (Breslow and Day, 1980, p. 196; Kleinbaum, Kupper and Morgenstern, 1982, p. 424; Schlesselman, 1982, p. 66, 196; Rothman, 1986, p. 321) For the specific factors considered here, this comparison would assess whether the association between adult ETS exposure and lung cancer is of the same magnitude in two groups of never-smoking women: those with childhood

[5] This notation builds from the pattern presented in the previous footnote. The first subscript refers to the presence (a value of 1) of adult ETS exposure (the row factor). The second subscript refers to the presence (a value of 1) or absence (a value of 0) of childhood ETS exposure (the column factor). The second subscript being enclosed in parentheses indicates that the odds ratio is calculated using the stratum-specific unexposed group as the baseline. That is, the stratum-specific odds ratio for adult ETS exposure among those without childhood ETS exposure equals the odds ratio for those with adult but not childhood ETS calculated using as the baseline group those with neither adult nor childhood ETS exposure.

ETS exposure and those without childhood ETS exposure. If these two stratum-specific odds ratios are found not to be equal, then a statistical interaction is said to be present. As is shown below, Fontham et al. (1994 [Ex. 377]) appears to have executed such a comparison.

If a statistical interaction is present, then it is standard statistical practice not to calculate a summary measure of association for either variable. Breslow and Day (1980, p. 197) state that it makes "little sense" to do so. If a statistical interaction is present, then summary measures of association for either factor are not useful because they would not provide valid estimates of the magnitude of association for any subgroup of the population. In this situation, at least two odds ratios are needed to summarize the pattern of association for the joint exposure to the two factors.

A statistical interaction between adult and childhood ETS is present in the Fontham data set. However, Fontham et al. (1994 [Ex. 377]) still calculated and presented a single summary measure of association. The magnitude of this summary measure of association has an uncertain interpretation and provides misleading information regarding adult ETS exposure and lung cancer.

RESULTS

The data from Fontham et al. (1994 [Ex. 377]; Table 8) on the joint exposure to adult and childhood ETS are summarized in Table 1 for the self-respondents. Table 1(a) summarizes the number of never-smoking cases and controls for each combination of exposures. For example, there are 23 cases and 71 controls who reported neither adult nor childhood ETS exposure. Similarly, there are 235 cases and 724 controls who reported both childhood and adult ETS exposure. The numbers of cases and controls for each combination of childhood and adult ETS exposure are the basis for the odds ratios presented in Table 1(b) - 1(d).

Table 1(b) presents the odds ratios for the examination of the joint exposure of childhood and adult ETS exposures, as called for by the design of the study. According to standard epidemiological practice, the subjects with neither childhood nor adult ETS exposure are used as the baseline group. The following pattern is observed:

* Never-smoking women with both adult and childhood ETS exposure are at no greater risk of lung cancer than never-smoking women with neither adult nor childhood exposure (OR = 1.00; 95% CI = 0.61, 1.64).

* Never-smoking women with adult but no childhood ETS exposure are at no greater risk of lung cancer than never-smoking women with neither adult nor childhood exposure (OR = 1.00; 95% CI = 0.60, 1.67).

* Combining the two results stated above, among never-smoking women, adult ETS exposure is not associated with an increased risk of lung cancer, regardless of the presence of childhood ETS exposure.

* Never-smoking women with childhood but no adult ETS exposure are at a significantly *lower* risk of lung cancer than never-smoking women with neither adult nor childhood exposure (OR = 0.35; 95% CI = 0.12, 0.99). This statistically significant negative association is most likely an artifact of bias either in study design or data collection.

Table 1(c) summarizes the stratum-specific analyses in which odds ratios for adult ETS exposure are calculated within groups defined by the presence or absence of childhood ETS exposure. The data used to calculate the odds ratios in Table 1(c) are the same as the data used to calculate the odds ratios in Table 1(b). There are two important limitations of the stratum specific odds ratios presented in Table 1(c) that are revealed by comparison to the odds ratios in Table 1(b). In Table 1(c) it is not possible to detect that i) women with childhood but not adult ETS exposure are at a lower risk of lung cancer compared to women with neither ETS exposure (OR = 0.35, 95% CI = 0.12, 0.99); and ii) women with childhood and adult ETS exposure have the same risk of lung cancer as women with neither ETS exposure (OR = 1.00, 95% CI 0.61, 1.64). Recognizing these two limitations, the stratum-specific odds ratios have the following interpretation:

Among the never-smoking women with no childhood ETS exposure:

* There is no change in the risk of lung cancer (OR = 1.00, 95% CI = 0.60, 1.67) associated with adult ETS exposure. That is, adult ETS exposure is ***not*** associated with an increased risk for lung cancer. This is consistent with the findings in Table 1(b).

Among never-smoking women with childhood ETS exposure:

* The risk of lung cancer is higher for women with adult ETS exposure than for women without adult ETS exposure (OR = 2.86, 95% CI = 1.12, 7.29). From this analysis alone, it is not possible to detect (and Fontham et al. (1994 [Ex. 377]) do not tell the reader) whether this difference is due to those with both ETS exposures having a higher risk than expected or due to those with childhood but no adult ETS exposure being at a lower risk. It is only from the joint analysis of risk in Table 1(b) that one discovers that the elevated odds ratio (OR = 2.86) is due entirely to the significantly lower risk of lung cancer among women with childhood and no adult ETS exposure (OR = 0.35, 95% CI = 0.12, 0.99). In fact, 2.86 = 1.0/0.35, indicating that the entire increase in this stratum specific odds ratio is due to the significantly lower risk among women with childhood and no adult ETS exposure. The failure of Fontham et al. (1994 [Ex. 377]) to disclose this fact makes their analysis incomplete and their interpretation misleading.

Statistical Interaction:

* The odds ratio for adult ETS exposure is significantly different for never-smoking women with no childhood ETS exposure and for never-smoking women with childhood ETS exposure; that is, OR = 1.00 vs OR = 2.86, p-value = 0.054.

The same general patterns are observed for all respondents (Table 2) that are observed for self-respondents (Table 1). Among all respondents, never-smoking women with both adult and childhood ETS exposure are at a lower risk (OR = 0.91; 95% CI = 0.59, 1.40) of lung cancer than never-smoking women with neither exposure. (Table 2(b)) Despite this lower risk, these never-smoking women with both exposures have more than a two-fold higher stratum-specific odds ratio (2.31 = 0.91/ 0.39) of lung cancer compared to women with childhood but no adult ETS exposure. (Table 2(c)) Again, this significantly elevated stratum-specific odds ratio is due entirely to the never-smoking women with childhood but no adult ETS exposure having a significantly lower risk of lung cancer (OR = 0.39; 95% CI = 0.17, 0.92; Table 2(b)). The difference in the stratum-specific odds ratios for adult ETS exposure is marginally significant (that is, OR = 2.31 vs OR = 1.07, p-value = 0.090). The failure to reach statistical significance in this particular analysis does not detract from the conclusion of a statistically significant interaction between childhood and adult ETS exposure because the analysis that includes proxy-respondents is considered less reliable than the analysis based only on self-respondents.

Because of the statistically significant interaction between childhood and adult ETS exposure, it is incorrect and misleading to calculate a summary odds ratio for either adult or childhood ETS using all of these data. Summary odds ratios do not provide valid estimates for any subset of the population of either of the association of adult ETS exposure with lung cancer or of the association of childhood ETS exposure with lung cancer.

Instead of summary measures of association, it is necessary to use two odds ratios to summarize the observed pattern of the association of lung cancer risk with childhood and adult ETS exposures. According to standard epidemiological practice, each of the two odds ratios uses as the baseline group the never-smoking women with neither childhood nor adult ETS exposure. The first odds ratio measures the risk among those with childhood but no adult ETS exposure and equals 0.35 (95% CI 0.12, 0.99). The second odds ratio measures the risk among those with adult ETS exposure, regardless of their childhood ETS exposure, and equals 1.00 (95% CI 0.62, 1.63). The difference between these two odds ratios is statistically significant (that is, p-value = 0.03, OR = 0.35 vs OR = 1.00).

Summary odds ratios for adult ETS exposure (summarized across levels of childhood ETS exposure) are calculated (self respondents in Table 1(d); all respondents in Table 2(d)), even though it is incorrect and "makes little sense" to do so. (Breslow and Day, 1980, p. 197) These summary odds ratios are presented because Fontham et al. (1994 [Ex. 377]; Table 7) calculated odds ratios for dose levels of adult ETS exposure that were not stratified by childhood ETS exposure. The summary odds ratio is 1.33 (95% CI 0.87, 2.05) is for self-respondents. A value similar in magnitude to the odds ratio for workplace ETS exposure reported by Fontham et al. (1991 [Ex. 8-106], Table 6; 1994 [Ex. 377], Table 6).

This summary association (OR = 1.33) results from the incorrect combination of the stratum-specific odds ratios for adult ETS exposure among those without childhood ETS and among those with childhood ETS exposure (that is, OR = 1.00 and OR = 2.86 average to OR = 1.33). The summary odds ratio is elevated only because of the large stratum-specific odds ratio for adult ETS exposure (OR = 2.86) for those with childhood ETS exposure. This large stratum-specific odds ratio is due entirely to a significantly reduced odds ratio for those never-smoking women with childhood but no adult ETS exposure (that is, OR = 0.35, Table 1(b)). The bias that generated the reduced odds ratio for never-smoking women with childhood but no adult ETS exposure is also responsible for generating the elevated summary odds ratio (OR = 1.33) for adult ETS exposure.

Because of the statistical interaction, the never-smoking women with childhood but no adult ETS exposure cannot be included in the baseline group in the statistical analysis of the other categories of joint exposure to childhood and adult ETS exposure. The inclusion of these women in the baseline group artificially inflates the estimates of risk associated with any level of adult ETS exposure.

The analysis of the dose-response pattern for adult ETS exposure is presented in Table 3 for self-respondents. Never-smoking women with childhood but no adult ETS exposure are excluded from this analysis. Once again, the never-smoking women with neither childhood nor adult ETS exposure are used as the baseline group. Four categories of childhood ETS exposure are considered: 'No', 'Yes', 'No & Yes', and 'No & Yes & Don't Know.' The last category includes all the subjects analyzed by Fontham et al. (1994 [Ex. 377], Tables 7 and 8) except for the cases and

controls with childhood but no adult ETS exposure.[6] The following patterns are observed for the self-respondents (Table 3):

* The overall OR is approximately 1.00 in all situations, indicating no association. This is particularly relevant to OSHA's rulemaking because it indicates that adult ETS exposure (which includes workplace ETS exposure) is not associated with an increased risk of lung cancer.

* A consistently increasing dose-response pattern is ***not*** observed.

* Using all the available data, the largest association (OR = 1.17; 95% CI 0.71, 1.95) in the highest dose group is lower than the average (albeit, biased) association (34% increase) for workplace ETS exposure reported by Fontham et al. (1991 [Ex. 8-106], Table 6; 1994 [Ex. 377], Table 6). This largest odds ratio is counterbalanced with the OR = 0.66 (that is, a 34% reduction in risk!) observed for those with the lowest level of adult ETS exposure. This type of pattern is consistent with a difference in the recall of the intensity of adult ETS exposure between cases and controls.

The same patterns are observed for all respondents (Table 4) as are observed for self-respondents (Table 3). Among the most complete set of subjects for childhood ETS exposure (that is, 'No & Yes & Don't Know,' rightmost column, Table 4), all but one of the ORs are below 1.00, indicating the absence of an increased risk of lung cancer associated with adult ETS exposure. The summary odds ratio (OR = 0.88) indicates a 12% reduction in the risk of lung cancer associated with adult ETS exposure. However, the statistical test for trend still achieves significance. This example demonstrates the fallacy of relying solely on the statistical test for trend when assessing the presence of a dose-response relationship.

The interaction between childhood and adult ETS exposure presented in Table 1 is demonstrated again in Table 5 from the perspective of the risk associated with childhood ETS exposure.

[6] No more detailed categorization of childhood ETS exposure can be considered in this analysis because of the limited data included in the article by Fontham et al. (1994 [Ex. 377]).

Among self-respondents, for each level of adult ETS exposure, previous childhood ETS exposure is not associated with any difference in risk of lung cancer (OR = 1.00, 95% CI 0.78, 1.29). Among never-smoking women with no adult ETS exposure, childhood ETS exposure is associated with a significantly lower risk of lung cancer (OR = 0.35, 95% 0.12, 0.99). The same general pattern is present for all respondents. (Table 6).

INCORRECT OR MISLEADING CONCLUSIONS IN FONTHAM ET AL. (1994 [EX. 377])

Fontham et al. (1994 [Ex. 377], p. 1758) incorrectly state that never-smoking women with *both* exposures were at a two-fold higher risk of lung cancer than never-smoking women with *neither* exposure. The specific misleading statements regarding adult ETS exposure in Fontham (1994 [Ex. 377]) include the following:

Misleading Statement	Correction/ Comment
"childhood exposure ... appears to modify the effect of subsequent ETS exposure during adult life." (p. 1758)	Fontham et al. correctly identified the presence of the interaction between childhood and adult ETS exposure. However, Fontham et al. incorrectly imply that those with both adult and childhood exposure are at higher risk than those with neither adult nor childhood exposure. This is not true, as indicated in Tables 1 and 2. The reason for the interaction (or "effect modification") is that those never-smoking women with childhood but no adult ETS exposure are at a significantly lower risk of lung cancer.
"(t)wofold increases in risk are observed at all levels of adult exposure for subjects who had any childhood household exposure compared with those who did not." (p. 1758)	The risk of lung cancer among women with adult and childhood ETS exposures is no higher than the risk for lung cancer i) among women with adult but no childhood ETS exposure, and ii) among women with neither adult nor childhood ETS exposure (Tables 1 and 2) The reference to a "twofold increase" apparently refers incorrectly to the difference in stratum-specific odds ratios. It is incorrect to imply that differences in stratum-specific odds ratios indicate differences in risk of a disease. (Tables 5 and 6)

Misleading Statement	Correction/ Comment
"Elevated risks associated with adult ETS exposure were observed in women with (trend P=.01) and without (trend P=.0005) childhood exposures, but the elevations in risk for women exposed during childhood were about twice as high as those without childhood exposure." (p. 1756)	Again, there is no elevated risk of lung cancer among women with adult ETS exposure (Tables 1 and 2). The statistical tests for trend do reach statistical significance. (Tables 3 and 4) But a consistently increasing dose-response pattern is ***not*** observed. The absence of a risk due to adult ETS exposure is not altered by childhood ETS exposure. (Tables 5 and 6)
"... the elevations in risk for women exposed during childhood were about twice as high as those without childhood exposure. At the highest level of exposure (48 adult smoke-years or more), an adjusted OR of 3.25 (95% CI 2.42 to 7.46) was observed among women reporting childhood exposure compared with 1.77 (95% CI 0.98 to 3.19) for those reporting no childhood exposure." (p. 1756)	Again, there is no elevated risk of lung cancer among women with adult ETS exposure, and the women with childhood and adult ETS exposure are at no greater risk of lung cancer than are women with neither adult nor childhood ETS exposure. (Tables 1 and 2) The odds ratios of 3.25 and 1.77 are adjusted odds ratio and, thus, could not be examined with the data currently available to the public. However, in the crude analysis, these *stratum-specific* odds ratios differ only because of the significantly lower risk for women with childhood but no adult ETS exposure. Fontham et al. have incorrectly interpreted differences in these stratum-specific odds ratios as reflecting differences in risk. (Tables 5 and 6)

Fontham et al. (1994 [Ex. 377]; Table 6) present crude odds ratios for each of the three components of adult ETS exposure: Household, OR = 1.17; Occupational, OR = 1.12; Social, OR = 1.42. It is misleading for Fontham et al. (1994 [Ex. 377]) to present the odds ratios for these individual sources of adult exposure without also presenting the joint analysis of each with childhood ETS exposure. It is reasonable to expect that the same sources of bias that generated an artificially elevated odds for adult ETS exposure (OR = 1.33, Table 1) would also influence the crude odds ratios for each component source of the adult ETS exposure.

Fontham et al. (1994 [Ex. 377], p. 1754) state that "(n)o statistical interactions were observed" but do not report their results specific to the statistical interaction presented in Tables 1 and 2. It may be that Fontham et al. generated the p-value 0.054 for the statistical test for interaction in Table 1 and, because it is greater than 0.050, concluded that statistical interaction was not present. Alternatively, it may be that, in lieu of the appropriate test for statistical interaction, Fontham et al. (1994 [Ex. 377], p. 1756) incorrectly substituted the examination of overlapping confidence intervals for the dose-specific/ stratum-specific odds ratios: "Although differences are approximately twofold, the CIs for the ORs at each level of exposure overlap."[7] Regardless of the reason, it is misleading for Fontham et al. to indicate that no statistical interactions were found.

The misleading presentation by Fontham et al. (1994 [Ex. 377]) has resulted in incorrect interpretations of these data by other scientists. Bayard (tr. 14715-14717) presented the results of the analyses of the joint exposure to childhood and adult ETS exposure from Fontham et al. (1994 [Ex. 377], Table 8, all respondents) and plotted the adjusted stratum-specific odds ratios. (Figure 1) The adjusted odds ratio could not be analyzed in this submission because the raw data are not available. The crude odds ratios for self-respondents (Table 3) that correspond to the adjusted odds ratios for all respondents presented by Bayard are plotted (Figure 2) using the never-smoking women with neither adult nor childhood exposure as the common baseline group for all exposure categories.

[7] This is not an appropriate method to assess statistical interaction, and Fontham et al. (1994 [Ex. 377]) provide no citation to support the use of such an approach. This method is not presented in the textbooks of Kleinbaum, Kupper and Morgenstern (1982) or Schlesselman (1982), the two sources cited by Fontham et al. (1994 [Ex. 377], p. 1754) for statistical methods.

With respect to the data in Figure 1, Bayard states:

> "Now if you just look at childhood exposure by itself, you don't find any increased risk but ... if you compare those who were exposed during childhood and adult with those exposed during adulthood only, you do find an increased risk and we think this is significant because it's similar to active smoking with the earlier the starting age the higher the risks." (p. 14716-14717)
>
> (specifically referring to Figure 1, his Slide 39) "If you weren't exposed during childhood, you get the little hollow circles. There's not much of an increase, depending on what your amount of smoke years as an adult was. There's a small amount. But if you were exposed during childhood, according to her data, and then exposed as an adult, the increase is significant. So there seems to be an effect of childhood exposure, a large effect of childhood exposure, if you were exposed as an adult." (p. 14717)

Bayard (tr. 14717) agrees with the analyses presented in this submission that ETS displays "not much of an increase" in risk for lung cancer among the never-smoking women without childhood ETS exposure (crude OR = 1.07, 95% CI 0.68, 1.68; Table 2(b) and 2(c)).

Bayard then compares the adjusted stratum-specific odds ratios for adult ETS exposure between the two groups: those with childhood ETS exposure and those without childhood ETS exposure. The problem is that Bayard interprets this comparison of stratum-specific odds ratios as a comparison of risks of lung cancer. Bayard indicates that women with both childhood and adult ETS exposure experience an increase in their risk that is "significant" or is a "large effect." Because of the difference in risk between the baseline groups for the sets of stratum-specific odds ratios, Bayard's interpretation is not correct. As shown in Figure 2 (crude odds ratios, self-respondents), for three of the four dose levels of adult ETS exposure, never-smoking women with childhood ETS exposure have a lung cancer risk that is lower than that for never-smoking women without childhood ETS exposure.

DISCUSSION

This submission re-examines the crude data presented in Fontham et al. (1994 [Ex. 377]) and provides analyses that demonstrate and quantify the presence of a study bias. The identified bias explains completely the crude association between adult ETS exposure and lung cancer that was reported by Fontham et al. (1994 [Ex. 377]). The use of the corrected estimate from Fontham et al. (1994 [Ex. 377]) of the association between adult ETS exposure and lung cancer (that is, OR = 0.99, 95% CI = 0.62, 1.58; Table 3) will result in a summary measure calculated from all relevant epidemiologic studies that is lower than the value previously reported to OSHA by Layard (1994 [Ex. 9-47603], OR = 1.09; 95% CI = 0.97, 1.22).[8]

The presence of statistical errors in published medical journals is not uncommon. OSHA's own consultant estimates that about half of all published medical articles contain such errors and advises the scientific community that peer-reviewers and editors cannot be relied upon to "have scrutinized every aspect of the manuscript, including the use of statistics." (Glantz, 1992, p. 7)

In the data set of Fontham et al. (1994 [Ex. 377]), it is necessary to exclude from the examination of adult ETS those never-smoking women with childhood but no adult ETS exposure because they experience a significantly lower risk of lung cancer than do women with neither exposure. If these 5 cases and 44 controls among the self-respondents are excluded (Table 7), then there is no association between lung cancer and adult ETS exposure (OR = 0.99; 95% CI = 0.62, 1.58). The statistical test for trend with dose achieves significance. However, the pattern of the association is not consistent and could be due to differences in the recall of intensity among cases and controls with adult ETS exposure. A similar pattern is observed for all respondents. (Table 8)

It is not clear which specific factors are the source of the bias in the Fontham study. It is clear that, whatever these factors are, they generate a bias that is manifest in at least two ways:

[8] The summary value reported by Layard (1994 [Ex. 9-47603]) used the value OR = 1.29 (95% CI 1.04, 1.60), the same value as used by OSHA's consultant (Brown, 1995 [Ex. 340-1787], p. 2-2).

* Lower estimated risk of lung cancer among women with childhood but no adult ETS exposure (OR = 0.35, a reduction in risk by a factor of 2.8, for self-respondents); and

* Higher estimated risk of lung cancer among women with adult ETS exposure (OR = 1.33, an increase of approximately 33%, for self-respondents).

The bias has now been tracked to a subgroup of the study population and shown to result in a spurious association. Without access to more detailed information on the study design and the raw data set of the study by Fontham et al. (1994 [Ex. 377]), it may not be possible to identify with greater certainty the exact source of the bias.

These two manifestations of the same source of bias can be viewed as two sides of the same coin. The identification of the factors that are the source of the bias in this study will, it is expected, explain the lower estimated risk of lung cancer among women with childhood but no adult ETS exposure and, consequently, the higher estimated risk of lung cancer among women with adult ETS exposure.

Because of the bias identified in this re-analysis of the Fontham data, it is necessary to correct the estimated odds ratio for each of the adult sources of ETS exposure presented in Fontham et al. (1994 [Ex. 377]); that is, spousal, household, workplace and social (Fontham et al., 1994 [Ex. 377], Tables 2, 3 and 6). This adjustment is expected to reduce each of these estimated relative risks. Unfortunately, Fontham et al. (1994 [Ex. 377]) have not provided the data in their publications to allow these adjustments to be made.

INTEGRATION WITH OTHER FINDINGS

Brownson et al. (1992 [Ex. 8-36]) and Fontham et al. (1994 [Ex. 377]) are the two largest case-control studies of lung cancer and ETS exposure. Both studies were designed specifically to assess childhood and adult ETS exposure. Both studies were federally funded by the National Cancer Institute. These two studies represent a large part of the federal government's effort to conduct original research to address this issue. It is appropriate to conduct a thorough analysis, review and interpretation of these studies to assess their relevance and contributions to the

setting of federal policy on ETS exposure. Unfortunately, as explained below, influences directed to the identification and reporting of an association between ETS and lung cancer may have affected the reporting of the results from these two studies.

The data in Brownson et al. (1992 [Ex. 8-36]) differ substantially from the conclusions stated by the authors. In some instances, the difference between the stated conclusions and the data can be identified through careful analysis of the information provided in the published article. In others, it is necessary to conduct analyses on the raw data collected in the study. For example, in analyzing their data, Brownson et al. (1992 [Ex. 8-36]) report:

> "no elevated lung cancer risk with passive smoke exposure in the workplace."
>
> "little evidence of increased risk associated with passive smoke exposure in childhood"
>
> "no evidence of interaction between exposure during the two periods" of childhood and adulthood
>
> "When analyses were limited to direct interviews, no clear pattern of increase or decrease in risk estimates was apparent" for adult household and spousal ETS exposures.

Despite these negative findings, Brownson et al. (1992 [Ex. 8-36], Abstract) concluded that their data "suggest a small but consistent increased risk of lung cancer" due to ETS exposure from a spouse. To support this conclusion, Brownson et al. (1992 [Ex. 8-36]) presented the results from the less reliable data on household ETS exposure that included proxy interviews and did not present quantitative results for workplace ETS exposure. Brownson et al. (1992 [Ex. 8-36]) avoided provoking questions regarding the contradictions between their conclusion and the data by neglecting to present the *quantitative* information on the absence of an association of lung cancer i) with workplace ETS, or ii) with household ETS among those with direct interviews. The quantitative results from both of these analyses indicate the absence of an epidemiological association between ETS and lung cancer (Butler, 1995 [Ex. 454]), and, thus, are not consistent with the stated conclusions in Brownson et al. (1992 [Ex. 8-36]). It was a full three years after the publication of Brownson et al. (1992 [Ex. 8-36]) that the data were made available to others

so that the more complete pattern of the absence of lung cancer risk for ETS exposure could be provided to federal agencies. These more complete, quantitative analyses were not available for the risk assessment of ETS performed by the USEPA (1992 [Ex. 8-311]) or to the USEPA Science Advisory Panel when it reviewed the USEPA's risk assessment of ETS.

A similar pattern of incomplete presentation and analysis has now been found in Fontham et al. (1994 [Ex. 377]). For this study there is the additional aspect of incorrectly stated conclusions that mislead readers to believe i) the risk of lung cancer is higher among women with childhood and adult ETS exposure compared to women with only adult ETS exposure, and ii) women with adult ETS exposure are at a higher risk of lung cancer compared to women with neither childhood nor adult ETS exposure.

As shown in this submission, but incorrectly or imprecisely reported by Fontham et al. (1994 [Ex. 377]), women with childhood and adult ETS exposure are at no greater risk of lung cancer than are women with neither exposure. The statistical interaction reported by Fontham et al. (1994 [Ex. 377]) results from a significantly lower risk of lung cancer among women with childhood but no adult ETS exposure. If this biased subgroup of subjects is removed from the comparison, adult ETS exposure is not associated with an increased risk of lung cancer, contrary to the highly publicized and relied upon reported findings of Fontham et al. (1994 [Ex. 377]).

Glantz (1992, p. 7), OSHA's own consultant, estimates that statistical errors are present in approximately half of the articles published in medical journals. He warns his student readers that they will confront "the confusion that arises when two seemingly comparable articles arrive at different conclusion" and that they may "often conclude that statistical analyses are maneuverable to one's needs, or are meaningless, or are too difficult to understand." (Glantz, 1992, p. 8) For controversial scientific issues, Glantz (1992, p. 8) states that "except when ... a paper includes the raw data, a reader cannot tell whether the data in fact support the author's conclusions or not."

Brownson et al. (1992 [Ex. 8-36]) did not provide the raw data to examine the association between lung cancer and ETS exposure in the more reliable data provided by the self-respondents. It was only through the acquisition of the raw data for this study that the

quantitative results of the absence of the association between ETS and lung cancer (only alluded to by Brownson et al. (1992 [Ex. 8-36]) were provided to OSHA. Further, it was through the re-analyses of the raw data published in the Fontham article (as encouraged by Glantz (1992, p. 8) that the contradiction in the findings between Brownson et al. (1992 [Ex. 8-36]) and Fontham et al. (1994 [Ex. 377]) are resolved.

A primary responsibility of all scientists is the forthright and complete presentation of the results of their studies. The "balancing" of the available information to reach a scientific or public policy decision is not the responsibility of the researcher but, instead, lies with scientific review boards and policy makers. (NRC, 1983 [Ex. 9-47553, Ref. 232], 1994) By providing less than complete and timely information from their studies, Brownson et al. (1992 [Ex. 8-36]) and Fontham et al. (1991 [Ex. 8-106], 1994 [Ex. 377]) have reduced the scientific community's access to relevant information; reduced the quality and completeness of the scientific data used in the federal risk assessment process; deprived federal policy makers of the full information collected using federal grant/contract resources; and made federal public health personnel, scientific review boards and others spend years of additional effort to extract a more complete perspective of the research on the health risks posed by ETS exposure. To avoid the uncertainty and confusion introduced by such practices, OSHA should obtain the raw data for all relevant epidemiological studies of ETS exposure and then make these data available to the public for confirmatory analyses.

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Table 1

Data from the Study by Fontham et al., (1994, Table 8),
Crude Association of All Lung Carcinomas with Adult and Childhood ETS Exposure,
Restricted to Self-Respondents

(a) # Cases / # Controls

		Childhood ETS Exposure: No	Childhood ETS Exposure: Yes
Adult ETS Exposure	No	23/71	5/44
	Yes	118/364	235/724

(b) Joint Examination: Odds Ratios & 95% Confidence Intervals

		Childhood ETS Exposure: No	Childhood ETS Exposure: Yes
Adult ETS Exposure	No	1.00 Baseline	0.35 (0.12, 0.99)
	Yes	1.00 (0.60, 1.67)	1.00 (0.61, 1.64)

(c) Stratified Analysis: Odds Ratios & 95% Confidence Intervals

		Childhood ETS Exposure: No	Childhood ETS Exposure: Yes
Adult ETS Exposure	No	1.00 Baseline	1.00 Baseline
	Yes	1.00 (0.60, 1.67)	2.86 (1.12, 7.29)

(d) combined Analysis: Odds Ratios & 95% Confidence Intervals

		Childhood ETS Exposure: All
Adult ETS Exposure	No	1.00 Baseline
	Yes	1.33 (0.87, 2.05)

Table 2

Data from the Study by Fontham et al., (1994, Table 8),
Crude Association of All Lung Carcinomas with Adult and Childhood ETS Exposure,
All Respondents (Self- and Proxy-)

(a) # Cases / # Controls

		Childhood ETS Exposure: No	Childhood ETS Exposure: Yes
Adult ETS Exposure	No	33/71	8/44
	Yes	182/365	305/725

(b) Joint Examination: Odds Ratios & 95% Confidence Intervals

		Childhood ETS Exposure: No	Childhood ETS Exposure: Yes
Adult ETS Exposure	No	1.00 Baseline	0.39 (0.17, 0.92)
	Yes	1.07 (0.68, 1.68)	0.91 (0.59, 1.40)

(c) Stratified Analysis: Odds Ratios & 95% Confidence Intervals

		Childhood ETS Exposure: No	Childhood ETS Exposure: Yes
Adult ETS Exposure	No	1.00 Baseline	1.00 Baseline
	Yes	1.07 (0.68, 1.68)	2.31 (1.08, 4.97)

(d) combined Analysis: Odds Ratios & 95% Confidence Intervals

		Childhood ETS Exposure: All
Adult ETS Exposure	No	1.00 Baseline
	Yes	1.24 (0.82, 1.65)

Table 3

Data from the Study by Fontham et al. (1994; Tables 7 and 8),
Crude Association of All Lung Carcinomas with Adult and Childhood ETS Exposure, Dose-Response Relationship
Excluding Cases and Controls with Childhood but No Adult ETS Exposure,
Restricted to Self-Respondents

Smoke Years of ETS Exposure During Adulthood	Childhood ETS Exposure?											
	No			Yes			No & Yes			No & Yes & Don't Know		
	# Cases/ # Controls	Crude OR	95% CI	# Cases/ # Controls	Crude OR	95% CI	# Cases/ # Controls	Crude OR	95% CI	# Cases/ # Controls	Crude OR	95% CI
>0	118/364	1.00	(0.60, 1.67)	235/724	1.00	(0.61, 1.64)	353/1088	1.00	(0.62, 1.63)	371/1113	0.99	(0.62, 1.58)
0	23/71	1.00	-	23/71*	1.00	-	23/71**	1.00	-	25/74**	1.00	-
1-11	23/90	0.79	(0.41, 1.52)	29/137	0.65	(0.35, 1.21)	52/227	0.71	(0.41, 1.24)	53/238	0.66	(0.38, 1.13)
12-28	28/97	0.89	(0.47, 1.67)	69/201	1.06	(0.62, 1.83)	97/298	1.00	(0.60, 1.70)	103/306	1.00	(0.60, 1.70)
29-47	36/97	1.15	(0.63, 2.10)	67/204	1.01	(0.59, 1.75)	103/301	1.06	(0.63, 1.78)	110/304	1.07	(0.65, 1.77)
>= 48	31/80	1.20	(0.64, 2.24)	70/182	1.19	(0.69, 2.05)	101/262	1.19	(0.71, 2.01)	105/265	1.17	(0.71, 1.95)
p-value trend		0.26			0.10			0.03			0.02	

* Substitutes cases and controls with neither adult nor childhood ETS exposure

** Excludes 5 cases and 44 controls with childhood but no adult ETS exposure

Table 4

Data from the Study by Fontham et al. (1994; Tables 7 and 8),
Crude Association of All Lung Carcinomas with Adult and Childhood ETS Exposure, Dose-Response Relationship
Excluding Cases and Controls with Childhood but No Adult ETS Exposure,
All Respondents (Self- and Proxy-)

Smoke Years of ETS Exposure	Childhood ETS Exposure?											
	No			Yes			No & Yes			No & Yes & Don't Know		
During Adulthood	# Cases/ # Controls	Crude OR	95% CI	# Cases/ # Controls	Crude OR	95% CI	# Cases/ # Controls	Crude OR	95% CI	# Cases/ # Controls	Crude OR	95% CI
>0	182/365	1.07	(0.68, 1.68)	305/725	0.91	(0.59, 1.40)	487/1090	0.96	(0.63, 1.47)	528/1115	0.88	(0.59, 1.31)
0	33/71	1.00	-	33/71*	1.00	-	33/71**	1.00	-	40/74**	1.00	-
1-11	33/91	0.78	(0.44, 1.39)	38/137	0.60	(0.35, 1.03)	71/228	0.67	(0.41, 1.10)	74/239	0.57	(0.36, 0.91)
12-28	41/97	0.91	(0.52, 1.58)	88/202	0.94	(0.58, 1.52)	129/299	0.93	(0.59, 1.47)	138/307	0.83	(0.54, 1.28)
29-47	54/97	1.20	(0.71, 2.04)	85/204	0.90	(0.55, 1.46)	139/301	0.99	(0.63, 1.57)	153/304	0.93	(0.61, 1.43)
>= 48	54/80	1.45	(0.85, 2.49)	94/182	1.11	(0.69, 1.80)	148/262	1.22	(0.77, 1.92)	163/265	1.14	(0.74, 1.75)
p-value trend		0.04			0.09			<0.01			<0.01	

* Substitutes cases and controls with neither adult nor childhood ETS exposure

** Excludes 8 cases and 44 controls with childhood but no adult ETS exposure

Table 5

Data from the Study by Fontham et al. (1994, Table 8),
Crude Association of All Lung Carcinomas with Childhood ETS Exposure for Each Dose of Adult ETS Exposure

Restricted to Self-Respondents

Smoke Years of ETS Exposure During Adulthood	Childhood ETS Exposure? No # Cases	# Controls		Yes # Cases	# Controls	Odds Ratio for Childhood ETS Exposure OR	95% CI
0	23	71	1.00 (baseline)	5	44	0.35	(0.12, 0.99)
> 0	118	364	1.00	235	724	1.00	(0.78, 1.29)
1-11	23	90	0.79	29	137	0.83	(0.45, 1.52)
12-28	28	97	0.89	69	201	1.19	(0.72, 1.96)
29-47	36	97	1.15	67	204	0.88	(0.55, 1.42)
>= 48	31	80	1.20	70	182	0.99	(0.60, 1.63)

Table 6

Data from the Study by Fontham et al. (1994, Table 8),
Crude Association of All Lung Carcinomas with Childhood ETS Exposure for Each Dose of Adult ETS Exposure

All Respondents (Self- and Proxy-)

Smoke Years of ETS Exposure During Adulthood	Childhood ETS Exposure?				Odds Ratio for Childhood ETS Exposure	
	No		Yes			
	# Cases	# Controls	# Cases	# Controls	OR	95% CI
0	33	71	8	44	0.39	(0.17, 0.92)
> 0	182	365	305	725	0.84	(0.68, 1.05)
1-11	33	91	38	137	0.76	(0.45, 1.31)
12-28	41	97	88	202	1.03	(0.66, 1.61)
29-47	54	97	85	204	0.75	(0.49, 1.14)
>= 48	54	80	94	182	0.77	(0.50, 1.17)

Table 7

Data from the Study by Fontham et al. (1994; Tables 7 and 8),
Crude Association of All Lung Carcinomas with Adult and Childhood ETS Exposure, Dose-Response Relationship
Impact of Excluding Cases and Controls with Childhood but No Adult ETS Exposure,
Restricted to Self-Respondents

Smoke Years of ETS Exposure During Adulthood	5 Cases and 44 Controls with Childhood but No Adult ETS Exposure?					
	Excluded			Included*		
	# Cases/ # Controls	Crude OR	95% CI	# Cases/ # Controls	Crude OR	95% CI
>0	371/1113	0.99	(0.62, 1.58)	371/1113	1.31	(0.86, 1.99)
0	25/74**	1.00	-	30/118	1.00	-
1-11	53/238	0.66	(0.38, 1.13)	53/238	0.88	(0.53, 1.44)
12-28	103/306	1.00	(0.60, 1.70)	103/306	1.32	(0.84, 2.10)
29-47	110/304	1.07	(0.65, 1.77)	110/304	1.42	(0.90, 2.25)
>= 48	105/265	1.17	(0.71, 1.95)	105/265	1.56	(0.98, 2.47)
p-value trend		0.02			<0.01	

* Fontham et al. (1994; Table 7)

** Excludes 5 cases and 44 controls with childhood but no adult ETS exposure

Table 8

Data from the Study by Fontham et al. (1994; Tables 7 and 8),
Crude Association of All Lung Carcinomas with Adult and Childhood ETS Exposure, Dose-Response Relationship
Impact of Excluding Cases and Controls with Childhood but No Adult ETS Exposure,
All Respondents (Self- and Proxy-)

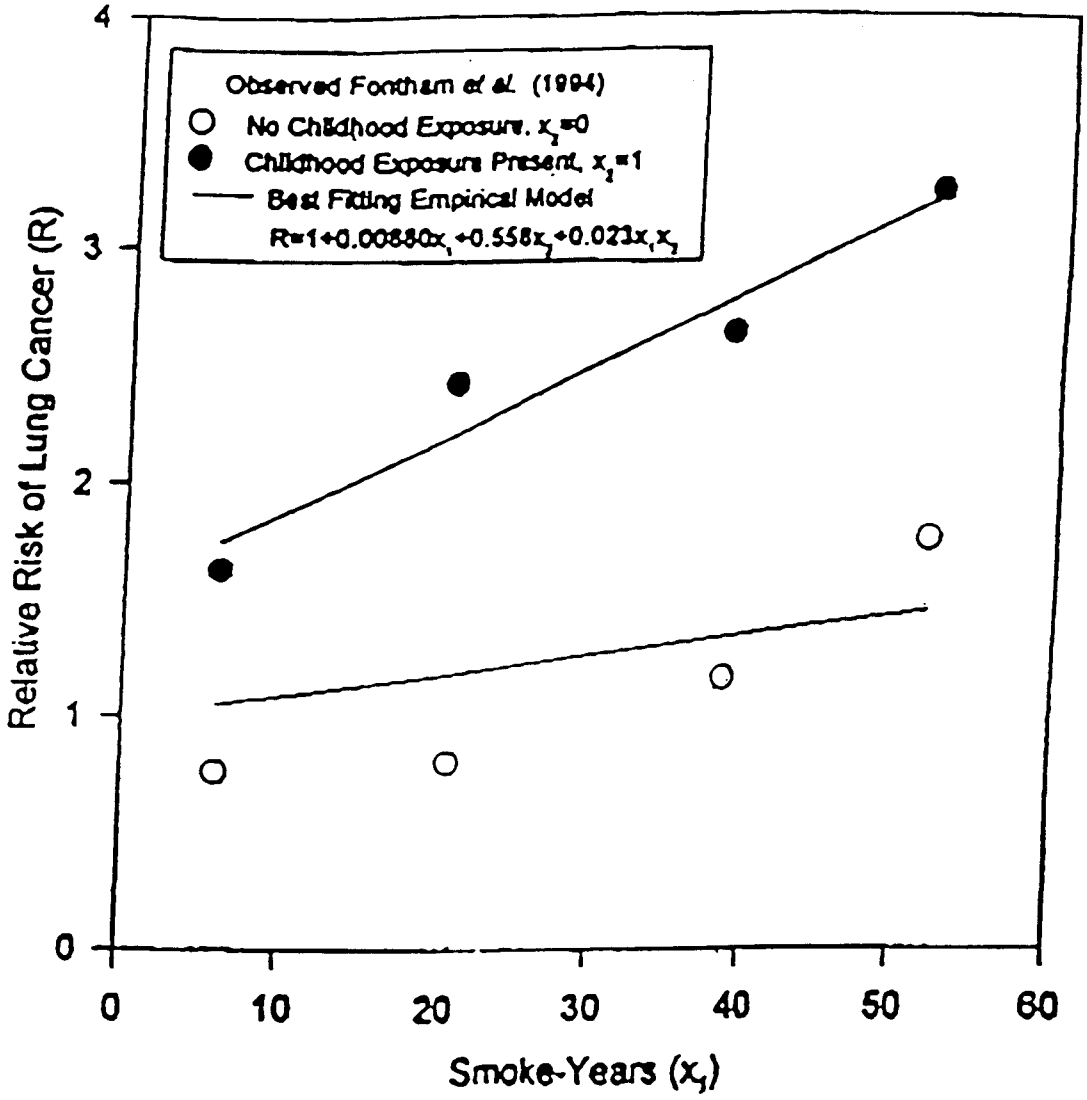
	8 Cases and 44 Controls with Childhood but No Adult ETS Exposure?					
	Excluded			Included*		
Smoke Years of ETS Exposure During Adulthood	# Cases/ # Controls	Crude OR	95% CI	# Cases/ # Controls	Crude OR	95% CI
>0	528/1115	0.88	(0.59, 1.31)	528/1115	1.16	(0.82, 1.65)
0	40/74**	1.00	-	48/118	1.00	-
1-11	74/239	0.57	(0.36, 0.91)	74/239	0.76	(0.50, 1.16)
12-28	138/307	0.83	(0.54, 1.28)	138/307	1.11	(0.75, 1.63)
29-47	153/304	0.93	(0.61, 1.43)	153/304	1.24	(0.84, 1.32)
>= 48	163/265	1.14	(0.74, 1.75)	163/265	1.51	(1.03, 2.23)
p-value trend		<0.01			<0.01	

* Fontham et al. (1994; Table 7)

** Excludes 8 cases and 44 controls with childhood but no adult ETS exposure

Figure 1

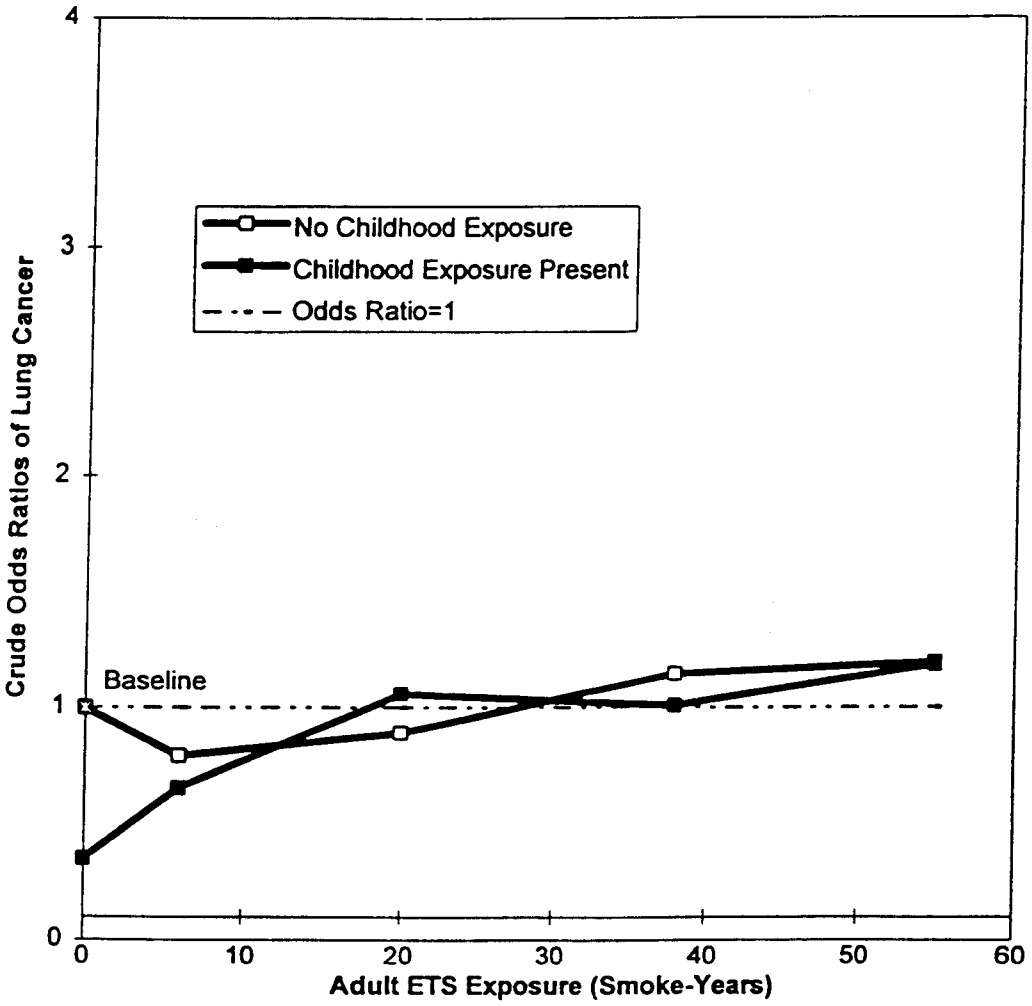
Slide 39 from Bayard (1995)



Weighted Multiple Regression Relative Risk of Lung Cancer Estimated from Presence or Absence of Childhood Exposure and Number of Smoke-Years of Adult Exposure

SLIDE 39

Figure 2



Crude Odds Ratios of Lung Cancer According to Childhood and Adult ETS Exposure, Self-Respondents, Fontham et al.(1994, Table 8)